

ANNUAL REVIEW OF PHYSIOLOGY

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# ANNUAL REVIEW OF PHYSIOLOGY

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## PREFACE

The present volume contains twenty-five reviews. To their authors we wish to express the thanks of this Committee, as well as of those who read the Review, for the fine spirit of collaboration they have shown and for the time expended in a most arduous task. As for three of the proposed reviews a word of explanation may be in order. The review on Blood Gas Transport, announced for inclusion in the present volume, has been postponed by request of the author and will appear in Volume IX. One on Senescence had not been received by mid-January and is presumed missing. A third review on Bioelectric Phenomena, announced for inclusion, was dropped from the list on recommendation of the prospective author.

The preparation of the reviews has proven difficult. In all cases the continuing unavailability of many foreign periodicals has been a serious handicap. Many topics of great interest to the physiologist are still under the ban of war-time controls imposed on scientific publications. Finally, the nature of the Review itself imposes a limitation of considerable perplexity and occasional embarrassment. We refer to the declared editorial policy of the Review. Encouragement is given only to the preparation of reviews which survey the important contributions of the preceding year or biennium, which appraise them critically, and evaluate with discrimination the present status of the subject. Comprehensive reviews in which the task of the author is one of compilation rather than of appraisal are deliberately eschewed. The value of such reviews is not in question. The Committee, however, confronted by the limitations imposed by publication space, aware of the great fertility and productivity of research in physiology, and convinced that the special function of this Review should be in criticism and appraisal, has deliberately adopted the policy formulated above. The author, in consequence, is free to go far in interpretation of the published data and to depart from the conclusions of others. Of necessity he can review but a portion of the papers before him

and must put aside many admirable contributions to the field either because they do not fall within the topics he has chosen to discuss or because they appear to be within the compass of another review.

To our readers we express our thanks for the patience they have shown in respect to procurement of the Review. Delays in publication have been trying but unavoidable. To our editorial assistants and to the George Banta Publishing Company we wish to convey our gratitude for the technical aid and cordial cooperation enjoyed throughout.

It is our pleasure to announce that the editorial duties incident to succeeding volumes will be carried by Professor Victor Hall as editor and Professors J. M. Crismon and A. C. Giese as associate editors.

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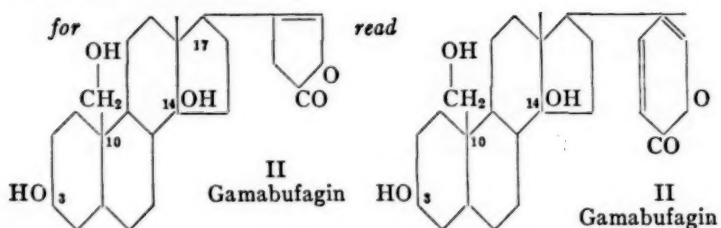
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## ERRATA

Volume VII, page 679:



page 711, column 3, line 24: *for* Crismon, C. S., 19, 182, 189, 190, 282, 419, 542, *read* Crismon, C. S., 19, 282, 419 and Crismon, J. M., 19, 182, 189, 190, 282, 419, 542

## EFFECTS OF ULTRAVIOLET RADIATION\*

BY ALEXANDER HOLLAENDER

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Interest in obtaining a better understanding of biological effects of ultraviolet radiation has been stimulated to a great extent during the last few years by the wide application that ultraviolet has found as a therapeutic agent (1) in genetics (120), in the study of the fundamental structure of living cells (23), and in its wide use in aerobiology (91). This review will discuss the effects of ultraviolet and visible radiation on a number of specific aspects; effects on higher plants and therapeutic applications will not be included.

Recently there has become available a number of inexpensive and efficient sources of ultraviolet light. Low pressure mercury vapor lamps with glass envelopes which emit about 80 per cent of their total and 95 per cent of their ultraviolet radiation at 2537 Å provide a handy tool for the study of the effects of radiation. These lamps have found wide use in preventive medicine and in industrial processes. The special usefulness of these lamps lies in the fact that 2537 Å is very close to the wavelength (2600 Å) which is most highly absorbed by nucleic acids. Relatively low intensities of 2537 Å will interfere with cell division and readily inactivate many disease agents which are not protected by other substances (53).

*Ultraviolet microscopy.*—The striking differences in the absorption spectra of proteins and nucleic acids have been discussed in a previous review (6). The improvements in the construction and use of the ultraviolet microscope by Caspersson (23) have made possible the quantitative determination of the concentration of nucleic acids and proteins not only in the nucleus (chromosomes) but also in the cytoplasm and have made it practical to follow the change in the concentration of these compounds during cell division (23, 24, 25). These improvements have enabled biologists to follow changes in living cells which involve as little as and often less than  $10^{-9}$  mg. of certain cell constituents. Since the appearance of the classical paper by Caspersson (23) a large number of reports

\* This review covers the period from 1943 to July 1945.

have come from his laboratory. Brandt (15) compares the appearance of yeast as seen with the ultraviolet microscope with that seen after staining. He discusses the structure of the nucleus and the appearance of granules which when seen in the ultraviolet microscope seem to contain nucleic acids but which do not take the Feulgen stain. The localization of the adenylic acids in stained muscle fibers is studied by means of ultraviolet absorption microscopy (25). Caspersson & Santesson (24) extended their studies to protein metabolism in the cells of epithelial tumors. This work with the ultraviolet microscope has made many important contributions particularly to physiological genetics. Its value in the problem of the effects of ultraviolet lies in the fact that it indicates quantitatively where the radiation is absorbed in the cell and it helps in recognizing the changes which take place during radiation in the distribution of protein and nucleic acid. Any future work on the effects of ultraviolet between 2000 and 3000 Å will profit by taking the results obtained by Caspersson and his co-workers into consideration.

Lavin (70) describes a simplified ultraviolet microscope which uses a low pressure mercury vapor lamp combined with a filter which supplies almost pure radiation of 2537 Å. The exclusive use of a single wavelength limits its value by making it impossible to obtain absorption spectra. However, the use of sufficient numbers of wavelengths permits a detailed spectral analysis of living cell constituents (see Caspersson). The ultraviolet microscope permits greater magnification and more detailed observation of structure in living cells than is available with the "visible" microscope. Hoagland, Shank & Lavin (52) applied this instrument to a study of specific lesions in muscle in subjects with progressive muscular dystrophy. Harvey & Lavin (50) in comparing the localization of nucleic acid in the egg of *Arbacia punctulata*, normal and centrifuged, found the same picture after staining as was revealed by photographs taken with 2537 Å. Mitchell (90), after describing certain modifications of the ultraviolet microscope, discusses the effects of x-rays on tissue cells. It appears that x-rays interfere with nucleic acid metabolism. The amount of ribonucleic acid in the cytoplasm increases and the amount of thymonucleic acid in the nucleus decreases after x-radiation. It would be interesting to see whether the same phenomenon takes place after ultraviolet irradiation.



A method which might be useful in ultraviolet microscopy has been employed by Goncalves (44) for directly determining the diffusion and absorption of radiation in turbid media. He made use of a formula developed by Wurmser (121) for the determination of absorption of pigments in cells. Anslow has reviewed the absorption spectra of biologically important compounds such as vitamins, proteins, steroids, etc. (3).

*Proteins and viruses.*—Very little additional information has become available during the last few years about the effects of ultraviolet radiation on cell constituents. The irradiation of horse serum and human serum and certain protein fractions of the latter results in increased viscosity, a decrease in colloid osmotic pressure and homogeneous electrophoretic mobility, and indicates that the major effect of 2537 Å on proteins is the unfolding and subsequent splitting of the protein molecules (33). Clark (26, 27) followed her earlier work on the basic changes in irradiation and heat inactivated egg albumin with a study of the effects of urea, radiation, and heat on the denaturation of crystallized egg albumin. Denaturation of albumin by radiation, urea, or heat is accompanied by an increase in optical rotation but not by association or dissociation within the pH range where aggregation follows denaturation. Further studies of the effect of ultraviolet on protein surface layers have been described by Dognon & Gougerot (35).

Since viruses, as far as their chemical composition has been determined, have in most cases proved to be nucleoproteins, it would be expected that their inactivation spectra would resemble the absorption spectra of typical nucleoproteins. Hollaender & Oliphant (61) reported a high sensitivity of influenza virus at 2650 Å with a decreased sensitivity at shorter and longer wavelengths. Similar inactivation curves have been reported for vaccine virus (98) and bacteriophage (39). In contrast to these inactivation curves, the viruses of typical tobacco mosaic (59) and Roux' sarcoma (109) show a slight maximum at 2600 Å and very much increased sensitivity at shorter wavelengths. Influenza and vaccine virus and bacteriophage have been reported to contain mostly desoxyribosenucleic acid and the tobacco mosaic and Roux' sarcoma to contain mainly ribosenucleic acid (61). It appears that ribosenucleic acid is less sensitive to 2537 Å irradiation than desoxyribosenucleic acid (47).

Lea *et al.* (71) found that the effect of gamma rays is independ-

ent of the tobacco mosaic virus concentration when the concentration is high but the effect is more pronounced when the concentration is low. Similar effects of x-rays on bacteriophage have been found by Luria & Exner (80). It appears that the low concentration effect is indirect and is probably caused by changes in the suspension medium. No such indirect effects have been reported to result from ultraviolet radiation.

Influenza vaccine produced by inactivating influenza virus by ultraviolet radiation was found to be not superior to the vaccine obtained by chemical methods of inactivation (84, 107). The ultraviolet irradiation of blood obtained from monkeys experimentally infected with poliomyelitis did not modify the course of the disease in subsequent infections produced by further inoculation of this blood into experimental animals (115). McKinsty & Reading (83) reported that the SK-mosaic strain of the virus may be inactivated by controlled irradiation and that this inactivated product is usable for immunizing purposes. Mice may be thus protected against 100 to 10,000 M.L.D. of the active virus. Milzer, Oppenheimer & Levinson (89) inactivated polio virus in a thin layer which was irradiated by a high intensity mercury vapor lamp. This treatment inactivates the virus in less than one second. Mice inoculated with two or three doses of this inactivated material developed significant resistance to intracerebral inoculation of the virus and to neutralizing antibodies. Earlier tests of the same type have been described by Jungeblut (67, 68).

The development of improved methods for the study of bacteriophages, and a better understanding of the means of phage attack on bacteria have made this virus-like agent a good tool for the study of the effects of radiation in the borderline field between viruses and bacteria (34, 78). Ultraviolet irradiated  $\gamma$ -coli phage interferes with alpha-phage and normal gamma-phage action, and also inhibits growth of bacteria without killing them. Continuous irradiation of this phage will destroy this property (79). This interference of ultraviolet inactivated particles with the function of the normal untreated agent has also been observed in the use of ultraviolet inactivated influenza virus (51). Those bacteriophages which survive a limited exposure to 2537 Å radiation grow more slowly. Increased radiation energy increases this growth delaying effect, but x-rays do not produce it (77). Royer & Guelin (102) describe the effect of visible light on bacteriophage. They found

increased resistance to light with increase in size of the phage particle.

*Bacteria*.—Little new information has been reported recently pertaining to the effects of ultraviolet radiation with wavelengths shorter than 3000 Å on bacteria except in connection with air sterilization and the production of vaccines. Levinson and co-workers (72) describe quick inactivation, by the method previously mentioned (89), of *E. coli*, *E. typhosum*, *Staph. aureus*, *Strep. viridans*, and other bacteria. The uniform sterilization of serums, plasma, brain, and tissue suspensions with ultraviolet radiation is difficult because of the low penetrating power of bactericidal and viricidal radiation through such solutions. The length of time of irradiation of these suspensions has to be determined by the absorption spectra of these materials and by determination of size and composition of the ultraviolet absorbing particles. As yet this method cannot be used by untrained technicians (57).

The bactericidal effect of sunlight which has passed through window glass and of radiation emitted by fluorescent and tungsten lamps has been described (18, 38, 88). Miller & Schad (88) discuss the effect of such radiation on meningococci; others describe the effects on streptococci (18, 38). The wavelength range producing these effects lies between 3300 and 7000 Å. The effects of infrared radiation seem to be unimportant. All the work in these three reports was done with dried bacteria. The effects on liquid suspensions of *E. coli* of radiation from the 3500 to 4900 Å (more than 50 per cent at 3650 Å) region of the spectrum, isolated by means of filters from a high intensity mercury lamp, showed that it takes 10,000 to 100,000 times as much energy in this region than at wavelength 2650 Å to produce the equivalent killing effect. It was found also that the radiation effects in this region have a high temperature coefficient and that bacteria surviving this radiation show a long delay in cell division and an increased sensitivity to a balanced salt solution (55). The effect of radiation of 3500 to 4900 Å on the eggs of *Enterobius vermicularis* and *Ascaris lumbricoides* expressed itself in a delay in hatching of these eggs and, at increased exposure, in death of these organisms (66).

The importance of the region between 3500 and 4000 Å in its effectiveness on higher organisms might very well be more profound than is usually suspected (6). Reports published as early as 1893 (116) point out that the visible region of the spectrum might be

a good field for further investigation and that the biological activity of radiation is not limited to the ultraviolet part of the spectrum.

*Fungi*.—The effects of radiation from commercially available mercury vapor lamps on spores of *Aspergillus niger*, *Rhizopus nigrans*, and a number of unidentified spores are described (106). Further studies (56, 62, 63, 64, 82) have verified the fact that the maximum efficiency for fungicidal action and mutation production lies at 2650 Å, the region which is most highly absorbed by nucleic acids. Attempts at producing mutations with "desirable" properties for the purpose of obtaining strains with improved fermentation were fairly successful (56). The work of Beadle & Tatum (112, 113) on mutations in *Neurospora* produced by radiation has indicated the usefulness as tools in biochemical research of mutants which have certain biochemical deficiencies. Increased itaconic acid production by *Aspergillus terreus* (75, 95) and increased penicillin production by *Penicillium notatum* mutants have been described (56). Similar results have been obtained with *Penicillium notatum* mutants produced by x-rays (64) and by neutrons (94). Increased penicillin production has also been observed in cultures of *Penicillium notatum* grown in the presence of radioactive substances (65). The use of radiation for producing strains of microorganisms with certain desirable properties is a promising field and deserves further investigation (56).

In a comparative study of the effects of x-rays (103) and ultraviolet radiation (63) on *Neurospora crassa* it is suggested that ultraviolet effects are localized, whereas the x-ray effects are more diversified. The latter include chromosome breaks and rearrangements. This picture of radiation effects on this fungus fits the results obtained with other organisms (120). The rate of mutation production from ultraviolet radiation is linear up to certain energy values. With further increase of energy the mutation rate becomes more or less irregular. In contrast to this the mutation rate produced by increasing energies in the x-ray region follows a straight line relationship over most of the range (56, 103).

Giese reports a stimulative effect of ultraviolet radiation on yeast, which is noticeable immediately after treatment in a limited number of cases, but the outstanding effect is a retardation of respiration (40, 41, 117). It is possible that the effect on respiration described by Giese is similar to the growth inhibition effect of ultraviolet radiation on bacteria; the organisms show a few divisions

immediately after irradiation, followed by an extended "lag" phase (66).

The interesting results obtained by studying radiation-produced mutations in fungi has stimulated similar investigations with bacteria. Braun (16) describes the effect of ultraviolet radiation on the dissociation of *Brucella abortus*, in which the *S* type can be made to change into *R* type colonies; but the change of *R* type into *S* type colonies is not observed. Lethal and dissociative effects of x-rays on *Staph. aureus* and *Serratia marcescens* are discussed by Haberman (48). Toxin formation is also affected. More detailed studies on the effects of x-rays on *E. coli* and *Acetobacter melanogenum* indicate that it is possible to produce in bacteria mutations of a nature similar to those produced in *Neurospora*, i.e., mutations which are unable to utilize certain incomplete media which suffice for the growth of normal organisms (31, 46, 100).

*Higher organisms.*—Giese (42) studied the effects of monochromatic ultraviolet radiation between 2483 and 3650 Å on well-fed and starved paramacia. He reports that the action spectrum for the retardation of division is similar to the absorption spectrum of a typical nucleic acid. The action spectrum for the retardation of ciliary movement resembles closely the absorption of a typical protein. This indicates that the first effect is probably on the nucleus and the second on the cytoplasm. In an interesting investigation (32) of the effects of monochromatic ultraviolet radiation on the chick embryo it was found that low intensities of radiation would inhibit the folding process in neural tube formation before interfering with cell division. The photochemical efficiency curve for this interference is very similar to the absorption spectra of certain sterols, particularly those which are thought to be the precursors of vitamin D. Only inhibiting effects of radiation from a low pressure mercury vapor lamp and several monochromatic wavelengths between 3660 and 2350 Å on the entire eggs and explants from portions of the egg were reported (105). The stimulation of the biopotential of the hen's egg by x-rays and 3100 Å to 3650 Å radiation was described by Romanoff (101). Eggs of *Strongylocentrotus purpuratus* irradiated on one side with 2537 and 2483 Å radiation showed upon fertilization asymmetrical membrane formation with suppression of this membrane on the irradiated side (96).

Metz (85) found that *Arbacia* fertilizin which had been inacti-

vated by x-rays (as evidenced by loss of its agglutinating power for sperm) inhibited the agglutination of sperm by normal fertilizin. Similar results were obtained with *Patira* fertilizin (86).

Nonspecific nuclear and cytoplasmic changes are observed in the photodynamic action of neutral red on embryonic chick cells. Photodynamic treatment interrupts mitosis, causes nuclear fragmentation and the formation of binucleated cells (108). The presence of fluorescent substances, chlorophyll, dibenzanthracene, methylcholanthrene, neutral red, and eosin, in tissue cultures causes dividing cells to become abnormal if exposed to light whereas resting cells are not affected within the energy and time limits used in these tests (73).

*Carcinogenic effects.*—Studies of the carcinogenic effects of ultraviolet radiation were extended considerably during the last three years (6).

Grady, Blum & Kirby-Smith (45) report that the predominant type of tumor appearing after ultraviolet irradiation of mice is a spindle cell sarcoma. Growth rates of ultraviolet-induced tumors are not correlated with the time of their appearance, age of the animal, or recency of exposure, but the greater part of tumor cell growth is controlled by the growth rate of the surrounding tissue (10). The wavelength 2537 Å seems to be less effective in inducing tumors in mice than other wavelengths. Apparently a greater part of this wavelength is absorbed in the corneum and cannot penetrate to the viable cells (13).

By the use of cut-off filters Blum (7) found that wavelengths around 3000 Å are the most effective and he speculates about the substances affected by this radiation. The intensity of this radiation is not critical after a definite threshold value has been reached (6). Neoplasms and other lesions can be induced in the eyes of mice by ultraviolet radiation. The cornea is most directly affected while the iris and lens may be involved secondarily (74). Studies conducted by means of interrupted exposures indicate that initial changes fortelling carcinogenesis appear very early. Tumors may not appear during the lifetime of the treated organism if exposure is discontinued too soon (9). If a susceptible strain of mice is used the incidence of pulmonary tumors in those irradiated with ultraviolet is lower than in unexposed mice. This is probably due to the fact that cutaneous tumors show up before pulmonary tumors have the opportunity to appear (11).

Bain & Rush (4) succeeded in locating the wavelengths of carcin-

ogenic ultraviolet light by means of filters. The wavelength range 2800 to 3400 Å is more effective in producing tumors in mice when given at low intensities over long periods than when given at high intensities (4). Exposure to radiation at 35 to 38° C. was more effective in tumor production than exposures conducted at room temperature or 3 to 5° C. (5).

Ultraviolet irradiated benzpyrene inhibits urease activity. One of the mechanisms involved is probably hydrogen peroxide production (85).

*Mitosis.*—The mechanics of the effects of ultraviolet on mitosis is of considerable interest because such information is very useful in the further understanding of radiation effects. There are several biological materials available in which the chromosomes are not surrounded by excessive amounts of material which might protect them against the radiation and in which mitosis can be followed readily. *Tradescantia* pollen grains are good material for such studies because the ultraviolet penetrates the pollen tube readily. Swanson (110) describes the effect of ultraviolet radiation on these pollen grains (2537, 2967, and 3022 Å). Chromatid breaks induced by 2537 Å are proportional to dosage. The prophase becomes progressively more resistant to exposure over some time. Pretreatment of pollen tube chromosomes with radiation of 2537 Å inhibits all the visible breaks usually produced by x-radiation, but treatment with ultraviolet after x-radiation has no effect. It is suggested that the ultraviolet produces changes in the chromosome matrix which results in greater resistance to x-rays (111).

The grasshopper neuroblast is another material which has proved very useful for study of the effects of radiation on mitosis. This material can be treated and observed in an artificial culture medium. The early prophase is the stage which appears to be most sensitive to 2537 Å radiation. Whereas the preliminary retarding effect of x-rays leads to a compensatory stimulative effect, or simulates such, the slowing down effect of ultraviolet is not followed by a compensatory speed-up of mitosis (21). The effect is the same whether the radiation is given continuously during one second, continuously over 1500 seconds, or intermittently over 1500 seconds. However, if the energy is increased sufficiently to lower the mitotic ratio to less than one-third of normal, then high intensity is more effective than the low intensity in decreasing the number of mitoses (22).

The wide use of low pressure mercury vapor lamps (see below)



and the extension of welding processes in industry has made the damaging effect of radiation on the eye by wavelengths shorter than 3000 Å an important problem (97, 104). As far as the effect of radiation of 2537 Å is concerned most of this is absorbed by the cornea (13). Since the cornea is rich in mitotic cells, a study of the influence of radiation on mitosis should be applicable to an understanding of the effect on the eye. As a matter of fact mitosis is retarded in irradiated rabbit and rat eyes. However, special methods will have to be developed for following mitosis in the cornea before progress in such studies can be made (69).

*Irradiation of blood.*—The use of ultraviolet for the treatment of blood by the "Knott Technic" has been discussed in a number of publications. Freshly removed blood is exposed in a special quartz chamber to radiation of a water cooled medium pressure quartz mercury vapor lamp. After irradiation the blood is returned into the body of the patient. This method has been reported to be efficient in the control of bacterial infection, in infections caused by virus and virus-like organisms, in increasing the efficiency of oxygen exchange mechanisms, and in producing profound effect on the autonomous nervous system (87). This problem has been discussed critically by Bradley (17) who recommends additional work to clarify the problem. The low penetration of bactericidal ultraviolet radiation in blood led Blundell *et al.* (14) to investigate the "Knott Technic" for its effects on the survival of bacteria and toxins in blood, peptone, and saline. Ultraviolet treatment by the above technic has a slight effect on bacteria suspended in saline or peptone solution, but a negligible irradiation effect is found for bacteria suspended in blood, and no detoxifying effect is noticed for toxins suspended in blood. The striking effects of the "Knott Technic" which have been reported cannot be explained by the effect ultraviolet has on the bacteria or toxins suspended in the blood.

*Ultraviolet in air disinfection.*—The application of ultraviolet radiation (2537 Å) for disinfection in controlling airborne cross infection has found fairly wide use in schools, children's wards, and hospital operating rooms. Earlier developments in the field of aerobiology, the physical aspects of finding a good source of 2537 Å radiation, the routine measurements of intensity (Rentschler), and earlier applications of bactericidal radiations are discussed in the volume on "Aerobiology" published by the American Association for the Advancement of Science (91).



A simple ultraviolet meter which makes use of a photographic exposure cell combined with a fluorescent plate for determining the emission of 2537 Å radiation has been described (114). A more elaborate and highly sensitive instrument is discussed by Andrews & Ogden (2). Tests describing the effectiveness of ultraviolet radiation in reducing the number of airborne microorganisms have been further discussed (19, 20). The wide use of these lamps in industrial bacteriology is also described (20). In an interesting study on the effect of ultraviolet on tuberculosis, Lurie (81) was able to prevent experimental transmission of tuberculosis from infected to susceptible rabbits by irradiation. The reduction of the incidence of crossinfection of measles, chicken-pox, and mumps (partially) in day schools is discussed by Wells and co-workers (118). A number of investigators (37, 49) have also reported the effects of ultraviolet radiation on crossinfection in the operating room and the operating table, both of which are irradiated (37). Crossinfection in infants' and children's wards is often a serious problem and exhaustive studies on the successful use of ultraviolet radiation in such wards are described by Robertson *et al.* (99).

In the above-mentioned studies ultraviolet was used for irradiation of the upper air above eye level. It was also used as screens at doors and partitions. The reduction of the airborne bacteria in an occupied area depends upon the natural exchange of air between the irradiated and the nonirradiated area. A considerable number of microorganisms settle to the floor with the dust and lint and are raised into the air again by air currents and mechanical movements. For the purpose of reducing the number of these organisms "floor irradiation" was suggested (58).

The relatively high incidence of upper respiratory infections in new recruits, living in crowded quarters, about three weeks after entering military service has made training camps a good place for testing different methods for controlling airborne infections. Combined upper air and floor irradiation was employed in a large scale study (119) on the control of airborne crossinfection in the barracks of a Naval Training Center. During the first winter a reduction of 25 per cent of upper-respiratory clinical admissions was noted in the barracks irradiated with high intensity ultraviolet. Since ultraviolet cannot penetrate dust or dirt readily the future of its use probably lies in combining ultraviolet radiation with other sanitary measures such as treating floors and bedclothes with

oil. (For review see 92.) The use of ultraviolet for the reduction of crossinfection in crowded quarters in barracks, schools, and certain hospital rooms is still in an experimental stage because considerably more information is needed in regard to suitable installations, as well as mode and location of crossinfection.

There are several interesting physiological problems which have come to the fore in connection with the wide use of 2537 Å radiation in airborne disinfection. (a) What is the maximum amount of 2537 Å radiation to which men can be safely exposed for a given length of time? (b) What is the effect of continuous exposure of men to small quantities of radiation of 2537 Å? The Council of Physical Medicine of the American Medical Association has set 0.5  $\mu$ W, per sq. cm. for seven hours and 0.1  $\mu$ W per sq. cm. for twenty-four hours exposure as the highest permissible limit (30). These are values based on the experience of workers in the field who have noticed no detrimental effects upon equivalent exposure.

The effects of the ultraviolet on the eye are usually the first to be noticed on prolonged exposure because radiation of 2537 Å is considerably less effective in the production of erythema than are the longer ultraviolet wavelengths (29). By way of contrast the eye seems to be quite resistant to x-ray exposure (36). It is difficult to evaluate this problem experimentally. However, data discussed above, obtained from studying the effect of ultraviolet on mitosis, can be very useful.

New low pressure mercury vapor lamps with glass envelopes may emit significant amounts of ozone-producing radiation (shorter than 2200 Å). Since ozone is very toxic, lamps should be burned in an unoccupied room for at least one hundred hours before their general use, after which time, in general, the transmission of the glass will have changed to such an extent that the ozone-producing radiation is considerably reduced. However, it is not advisable to use these lamps in rooms where there is no fresh air supply available because a small amount of ozone may still be produced by the lamps even after considerable "burning in" (28).

A detailed review on "The physiological effects of sunlight on man" has just appeared (12). The extensive volume on *Medical Physics* (43) contains a number of chapters on the physical aspects as well as the physiological effects of ultraviolet radiation.

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## PHYSIOLOGICAL ASPECTS OF GENETICS<sup>1</sup>

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Genetic heterogeneity in any stock of organisms used for experimental work is of immediate physiological significance since it at once becomes important to determine to what extent the several genotypes have differential effects on critical reactions. The likelihood of confused or conflicting data from the use of untested strains has now come to be generally recognized. An increasing appreciation of this point, coupled perhaps with the fear that a lack of reference to its genetic aspects might brand an article as uncritical, has led to the appearance of minor, or sometimes even major, contributions to genetics in papers whose authors often were only incidentally concerned with the subject as such. The result is a large volume, in the aggregate, of incidental data of genetic import scattered widely through medical and biological journals, where the items may remain individually of small interest until such time as the literature can be combed with a view to obtaining a picture of the total physiological effects of an individual gene or group of genes. What such a picture might be is still far from clear. One question well to the fore at present is whether each gene makes one, and only one, consistent and specific contribution, perhaps as an enzyme, or whether the same gene may function at different times in different ways.

Much of the recent work bearing on this specific question was summarized in the preceding volume by Wright (1), who has himself made important contributions to the subject. During the succeeding twelve months further papers have appeared in this immediate field. One of them is a reinterpretation by Goldschmidt (2) of data of Stern (3) and Stern & Schaeffer (4), who had found that the gene *ci* which produces the "cubitus interruptus" effect in *Drosophila melanogaster* is recessive to its normal allele at 25° but partly dominant at 14°. However, through use of duplications and deficiencies, the original authors were able to study the effect of *ci* by itself, in diploid and in triploid combinations, as well as

<sup>1</sup> This review covers the period from September, 1944 to September, 1945.

in associations with each of three "normal" alleles. From the results it was inferred that *ci* by itself tends toward the production of normality since the effect of *ci ci* is more normal than that of  $-ci$  and less normal than that of *ci ci ci*, even though *ci* in conjunctions with  $+$  genes tends away from normality. This reversal of effect in different combinations and at different temperatures has been interpreted to mean that the gene reacts differently, or with different substrates, according to circumstances. Goldschmidt's alternative hypothesis would assume that all the genes consistently produce the same kind of substance, but that each allele does so in different amounts. Those combinations of genes whose additive effects fall above a certain threshold at the critical moment tend toward normality, while those which fall below that level tend in the opposite direction. By assigning arbitrary values to the effect of each allele and assuming a hypothetical threshold level, the expected effect in sixteen experiments agree with Stern's data in all but three: the combination of  $+^2 ci ci$  which should be third according to Goldschmidt's hypothesis being eighth in Stern's observations,  $+^3$  differing by five places in the two series, and  $+^4 ci$  by one. This would seem to leave the question of qualitative differences in the output of these genes still open. The same question is considered by Spencer (5) who finds that various combinations of alleles at the "bob" locus affect several different traits in *D. hydei* but that the gene-induced plus or minus deviations in one trait are not paralleled by variations in the same direction in other traits, as might have been expected from Goldschmidt's interpretation of the mode of action of the *ci* alleles.

Another gene in *Drosophila* that shows variability in expression is *bx-34e* which causes the halteres to develop in the direction of wings, the range being all the way from normal halteres to large flat wing-like structures with four veins. Villee (6) finds that application of heat beginning during the first five days after oviposition increases the degree of wing development. This adds another to a long list of genes whose effects appear to vary with temperature. At the bacterial level, Gowen (7) thinks that alternative genes may possibly differ in chemical structure but more probably in their capacity to produce larger or smaller quantities of a single antigen or endotoxin. Further evidence of specificity at the genic level in bacteria may be indicated in the finding of Neter (8) that while various strains of staphylococci differ in their



susceptibility *in vitro* to the bacteriostatic action of penicillin, tyrothricin, and streptothricin, their relative susceptibility to one of these antibiotics is not paralleled by similarly graded susceptibility to the others.

Ephrussi & Herold (9, 10) studying spectroscopic properties of eye pigments in flies think it probable that the different phenotypes of mutants in the white-eye series of alleles represent different levels reached by a single process—an hypothesis, they point out, which “distinctly runs along the lines of Goldschmidt’s general theory of gene action.” In *Drosophila melanogaster*, Lewis (11) finds that the several alleles of the gene *asteroid*, which influence eye form and other traits, show a different order of effectiveness depending on whether the same grouping is associated with *Star*, or its normal allele, in a very short “repeat” section of the chromosome in which these genes occur. In such cases, involving the position effect, the possible vitiating influence of most extraneous factors seems to be largely eliminated, but even if a gene were to produce a single substance, constant in amount and unvarying in chemical composition, it would still be impossible in most cases to prove that it did so without complete information on all other protoplasmic “substrates” that might influence the end result. In what is possibly a majority of cases, observed fluctuations lend themselves to a satisfactory tentative explanation on the assumption that the output of individual genes is constant but that the effect may be modified by various external and internal factors, including the products of other genes.

While the exact nature of the gene and its products is at the moment one of the central problems in genetics, most of this year’s crop of paper in the English language (the foreign literature is still almost wholly unavailable to the reviewer) bears on the question only indirectly. Papers selected for brief mention will be considered in the following overlapping and interrelated sections: Nature of the gene, Mutational changes, Chromosomal behavior, Rejuvenescence and hybrid vigor, Speciation, Sex, Embryology, Genetic differences in the reactions of adult animals.

*Nature of the gene.*—Until the riddle is finally solved there will inevitably continue to be a diversity of suggestions as to what the gene really is, a subject discussed from many angles by Gulick (12) in a review paper to which the reader may be referred. A well-known physicist, Schrödinger, has tackled the question in a

book (124) which is eliciting considerable discussion [Haldane (13), Manton (14)], and agrees with some earlier writers that recognition of the whole chromosome as a single molecule is consistent with an understanding of genetic phenomena. Like most students, however, he directs attention chiefly to gene-loci and mutations, which are discussed in the light of quantum mechanics. As has been noted in the earlier reviews of this series the possible interrelations, or even partial homology of genes, enzymes, and viruses, have appealed to the imagination of many investigators. To what extent it is possible to homologize intrachromosomal and extrachromosomal units calls for further clarification.

Darlington (15) in an attempt at a brief synthesis of knowledge in this field recognizes different levels of independence and self-determination among protoplasmic elements. Plastids, or plastogenes, which are apparently complex structures, he suggests may be caused to mutate by nuclear genes much as certain nuclear genes are known to cause other nuclear genes to mutate, as for example, the *Dt* gene which causes gene *a* to mutate to gene *A* in maize [Rhoades (16)]. Smaller, more pervasive elements, on the molecular level, are the plasmagenes. These are proteins "which can be made outside the nucleus and be inherited through the egg. . . . The virus is a similar protein which can be acquired later." Both plasmagenes and viruses are supposed to be continually arising *de novo* and evolving rapidly. Plasmagenes have rates of reproduction so varied that one plasmagene may virtually swamp another; thus, in effect, it may act as a kind of dominant. It would also seem to be implied that a plasmagene may sometimes mutate into a virus and strike out on its own. "The frontiers that exist between the studies of heredity, development and infection are thus technical and arbitrary, and new possibilities of analysis and experiment will arise when we have learned the password to take us across them."

A term to designate another type of "gene" has been proposed by Lindegren on the basis of his own work and that of his colleagues (17, 18, 19). This is the cytogene, a concept which grew out of studies on yeast. Lindegren finds this material with its diplophase and haplophase stages especially suitable for genetic exploration. One of the yeasts, *Saccharomyces carlsbergensis*, is capable of fermenting melibiose, while another one, *S. cerevisiae*, is not. The ability to ferment this sugar proves to be due, ulti-

mately, to two nonallelic dominant genes both present in the former species. Haploid segregants from hybrids between these two species show a one-to-one ratio between potential fermenters and nonfermenters, these differences persisting indefinitely in each clone. But when the segregants are all kept together from the first, and in the presence of melibiose, all of them can ferment the sugar; even the genetically negative clones continue to maintain this capacity when once acquired, so long as they are propagated in a melibiose-containing medium. This seems to mean that the enzyme melibiosylase produced normally in the cytoplasm of the fermenter strain can be transmitted to the cytoplasm of associated nonfermenter cells, which can then ferment the sugar and transmit the capacity to subsequent generations. Lindegren emphasizes that this adaptive and transmissible enzyme mechanism is dependent ultimately on a chromosomal background which results in the production of a presumed cytoplasmic protocytochrome that can be "impressed" by the melibiose to form the cytochrome, which is thenceforth inherited wholly apart from the nuclear mechanism. The difference between these two strains of yeast is that one has a genetically determined protocytochrome which can establish the appropriate cytochrome at any time, while the other can acquire the cytochrome only by a kind of inoculation. In either case the cytochrome itself is dependent on the presence of melibiose for its continued autosynthesis.

Similarly puzzling nuclear-cytoplasmic relations arise in *Paramecium aurelia* where Sonneborn in his earlier work found that the cytoplasmic substance "kappa" (which makes the medium toxic to other types), while normally present only in animals with the nuclear genes  $KK$  or  $Kk$ , cannot be initiated by the gene  $K$ . Consequently strains may be obtained which are even homozygous for  $K$  and still lack kappa; but if a little of the kappa can once be introduced it serves as a cytoplasmic "primer" and, provided the strain contains  $K$ , is produced in abundance from then on. It might perhaps have been surmised that there is some parallelism between the cytoplasmic kappa and a cytochrome in yeast, the one dependent on the constant presence of something from the nucleus, the other on something from the medium; but Sonneborn (20) has now found some cases in which both  $K$  and kappa are present without producing the usual "killer" effect. The situation is still not fully explained, but it has been possible

by increasing the number of new *K*-containing macronuclei formed at fertilization to reduce the amount of active cytoplasmic kappa, and this is interpreted to mean that a combination is effected at this time between *K* and kappa. If this is correct, it implies that kappa, an outside agent, becomes a part of a gene that in turn supplies to the cytoplasm a substance similar to itself in being able to combine with kappa and, when so combined, to synthesize more kappa.

With reference to genes and viruses Glaser (21) points to the theoretical attractiveness of certain space-lattice arrangements revealed in x-ray studies of the tomato virus as models for the structure and reproduction of units in both these groups, but emphasizes that, after all, in the living tissues the system must be in a dispersed rather than a crystalline form. Bowden (22) comments that the answer an investigator gives to the question as to whether viruses are living or nonliving usually depends on the methods he uses in his own investigation: in the test tube viruses behave as if they were protein molecules; in affected plants and animals their behavior is that of living organisms. Gulick (12), postulating that the primitive state of organisms may be presumed to have been little more than a single gene, somewhat like a virus, considers that the study of genes falls within the purview of those chemists who interest themselves in the character of megamolecules, but thinks chemistry has as yet contributed little to genetics beyond a very important pattern of thought. In concluding a discussion of the properties of viruses, Pirie (23) expresses the opinion that "no rigid distinction has been, or perhaps can be drawn between those systems conveniently referred to as 'living' and 'nonliving,' and no observation has so far been made on plant viruses which has any bearing whatsoever on this metaphysical or semantic problem." That this area of the subject is one of great interest and promise is evident, but it remains to be seen whether such terms as cytogene and plasmagene will prove to be in a sense figurative in their implication, or really indicative of a rapid approach to an enhanced understanding of chromosomal genes, and perhaps of a whole hierarchy of related functional units.

*Mutational changes.*—Because of the possibility of real or apparent pleomorphic effects of the same gene, and the frequent versatility of cytoplasmic reactions, definite identification of a new point mutation is often far from easy. When bacterial or even

virus cultures undergo marked changes in character, these changes are often interpreted as mutations, which are thought of as essentially comparable to the point mutations of higher forms. Such mutational changes have occurred in cultures of *Escherichia coli* studied by Luria (24). The bacteria are sensitive to two different viruses,  $\alpha$  and  $\gamma$ , in the presence of either of which the cultures are completely lysed—except that now and then small clusters of resistant cells remain. These groups are believed to be descended in each case from a mutant individual. Cultures of such cells are not lysed by the virus to which they are immune, but are lysed by the other one. The original bacterial strain may now be designated as B and the mutant as B'. When B' cultures are grown extensively in media containing the virus to which they are immune, e.g.,  $\gamma$ , occasionally a clear area appears in which even the B' cells have been lysed. From these areas a new virus  $\gamma'$  may be obtained and this will consistently lyse B' cultures. This is interpreted to indicate a mutation in the virus. The viruses  $\gamma$  and  $\gamma'$  act in the same way on B, but  $\gamma'$  can and  $\gamma$  cannot lyse B'. Parallel results were obtained with the other virus and its mutant. When tested with antisera from rabbits it was found that  $\gamma$  and  $\gamma'$  are serologically identical but distinct from  $\alpha$  and  $\alpha'$  (which similarly are identical with each other). While recognizing the lack of direct evidence of genes in bacteria and viruses, the author prefers to call these changes mutational because of their apparent spontaneous and random occurrence, their transmission, and stability. In passing it may be of interest to note a possible similarity to the alleles of higher forms in that the change from  $\alpha$  to  $\alpha'$  or from  $\gamma$  to  $\gamma'$  is sufficient to alter the function but not to change the "identity" of these units.

Demerec & Fano (25) report studies on the resistance of the same organism to seven different strains of bacteriophage, having investigated 377 new mutations and 364 mutants from lines already resistant to one or more of the phages. The rates of mutation are not the same against all types but they are of the order of  $10^{-7}$  or  $10^{-8}$ , and it is interesting to note that some combinations of mutants occur more frequently than do others. The strains do not differ systematically in growth rate yet may show minor cultural differences. Complex strains resistant to several phages may arise by a single mutational step or by the accumulation of several separate mutations.

In a somewhat similar way previously susceptible lines of bacteria may become immunized to the action of penicillin. Demerec (26) finds that a concentration of 0.012 Oxford units of penicillin has little effect on a particular strain of *Staphylococcus aureus*, but with increasing concentrations correspondingly larger numbers are killed until at 0.15 units all are eliminated. However, by propagating survivors from any of the lower grades, it is found that stocks with increased resistance can be produced. Such stocks retain their increased level of resistance if kept in the refrigerator or if passed through a series of penicillin-free broths. That the resistance is due to mutation and not to adaptation is indicated by a number of experiments such as dividing a single original culture into one large and several equal small subcultures and then after a time dividing the large culture into parts equivalent to each of the small cultures and testing them all simultaneously. In such tests it was found that the derivatives of the large cultures were essentially homogeneous while the small ones showed wide variations, as would be expected if mutations had been occurring at random. By selecting survivors from media which contained low concentrations of penicillin and by treating their descendants to higher concentrations of penicillin, an increase in resistance was built up by gradual steps, the indications being that the change was wholly a matter of mutation and not one of direct adaptation. There are apparently a number of different genes whose effects are cumulative and more than merely additive. In the end, strains were obtained which were to all intents and purposes completely resistant to penicillin. Appropriate tests with bacteriophage showed that these strains were actually derived from the original stock and were not contaminations. Spink & Ferris (27), on the other hand, find that *Staphylococcus* which has become resistant to penicillin in the human body produces a "penicillin inhibitor" which cannot be obtained from *Staphylococcus* made highly resistant *in vitro*. Resistance acquired *in vivo* they believe to be more enduring than (and apparently somewhat different from) that acquired *in vitro*. It is not yet entirely clear whether both mutation and adaptation are involved in some or all of these experiments. There is the same formal difficulty in interpreting the results of Severens & Tanner (28) who subjected *Eberthella typhosa* and two species of *Salmonella*, *pullorum* and *schotmülleri*, to solutions of sodium chloride, copper sulphate, and mercuric



chloride in strengths that would ordinarily inhibit growth, and were able to derive strains that were resistant to these concentrations. They think it most likely that these resistant forms descended from chance mutants, a belief which is strengthened by the fact that equally resistant cells are found at times in untreated cultures—an example perhaps of "preadaptation."

Gray & Tatum (29), using a somewhat different approach, subjected two forms of bacteria to x-ray treatment and induced mutations in them. One treated line of *Escherichia coli* was found to be deficient in its capacity to elaborate biotin, while another was similarly deficient in respect to thionine. In the other species, *Acetobacter melanogenum*, four induced mutants were obtained, one requiring for its adequate growth an artificial supply of serine or glycine, another adenine or adenosine, a third glycine, and a fourth leucine.

On a slightly higher biological level, but one in which chromosomal organization is still little known, Burkholder *et al.* (30) have studied genic function as revealed by capacities of various yeast cells to synthesize amino acids and vitamins. Among 163 species and strains they found 78 lines unable to synthesize biotin, 33 thiamine, 30 pantothenic acid, 15 inositol, 13 nicotinic acid, and 13 pyrodixine. All of them could synthesize riboflavin. The Lindegrens (31) mated a strain of yeast which is capable of synthesizing biotin and pantothenic acid, but not pyrodixine, with one which cannot synthesize the first two but produces the latter in adequate amounts. The hybrid was able to synthesize all these substances in abundance. Similarly *Saccharomyces globosus* which can produce pantothenic acid but not thiamine, and *S. cerevisiae* which can produce thiamine but not pantothenic acid, gave a hybrid which could synthesize both. A considerable series of experiments indicates that in such crosses heterozygotes are about as efficient as homozygotes. It is interesting to find that deficient strains segregate out from heterozygous positive strains.

Beadle (32) reports five ultraviolet-light-induced mutants in *Neurospora* which could not synthesize inositol, and shows that the growth rate of these defective lines provides an accurate method for assaying inositol in media where its concentration falls between 5 and 30  $\mu$ g. per 20 ml. Further studies of this general order are reported by Beadle, Tatum, Horowitz, and their associates (33 to 36). It is shown that in *Neurospora* the synthesis of living matter

is under genic control and that in general there is a one-to-one correspondence between genes and chemical reactions, the number of genes involved in a final synthesis being approximately equivalent to the number of steps involved chemically. In some of these syntheses, intermediary products are formed which it would seem could at no time have had any direct biological value of their own and hence could not have been subject to favorable natural selection. This makes it difficult to understand how some of these gene-controlled chemical sequences could have evolved. Horowitz (37) makes the suggestion that the first appearance of anything so complex as living matter must imply a pre-existing highly complex chemical environment but that as the necessary chemical compounds became rare or exhausted, continuation of life depended on the fortune of the organism in acquiring by mutation the ability to synthesize these compounds for itself. Thus it might be that the course of evolution has been the exact reverse of the steps in present day biochemical syntheses.

With still higher forms, recognition of the precise function of individual genes becomes more difficult, partly because of the greater complexity of the tissues and the greater number of genes which are likely to influence in one way or another the manifestation of a somatic trait. Even relatively simple cases generally show some complexities. In *Ephestia*, according to Casperi (38), animals homozygous for the gene *a* have reduced pigmentation not because of lack of tryptophane, of which they have an excess, but because of their inability to oxidize it. Some strains of barley are resistant to the mildew *Erysiphe graminis*, but not all for the same reason. According to Briggs (39) there are seven different genes for resistance, two of them linked. Such genes undoubtedly have a selective value, but with leaf shape in cotton, where Stephens (40) finds four alleles variously distributed among different species, it turns out that these units are especially influenced by genes controlling flowering habit; and, consequently, while leaves are not directly subject to selection, they do show a non-adaptive trend which is only a by-product of selection in another system. "Canalized" systems may thus be established which are little affected by environmental factors. On the basis of this and other studies on the *Malvaceae* the same author (41) is led to lay special stress on "gene tracts," i.e., the expression of a gene over a period of time. In these plants the leaves pass through a rather definite succession



of forms some of which, especially the terminal, may never be realized; this is only one instance where the actual phenotypic expression of a gene may represent only a fraction of its potentialities. A trait may deviate widely in the plus or minus direction largely through the intervention of modifiers or polygenes. Svardson (42), who attempted to change the number of fin rays in *Lebistes* by selection and met with some slight success, also subscribes to the Mather concept of "polygenic inheritance." On the other hand, there are many relatively uncomplicated cases of essentially monofactorial inheritance. For example, Hays (43) by properly planned matings easily segregated the autosomal *E* and the sex-linked *E'* genes for early maturity in the common fowl and found that in the absence of both, sexual maturity was attained at from 250 to 300 days, with *E'* alone in from 190 to 200 days, and with both *E'* and *E* in from 170 to 175 days. Most studies in this field are either of little immediate physiological interest or relate specifically to one of the special phases of embryology or pathology.

*Chromosomal behavior.*—Studies of chromosomes as units have continued to be partly experimental, partly observational. Darlington & La Cour (44), considerably extending their earlier work on analyses of x-ray effects in relation to euchromatin and heterochromatin, maintain that an important time factor has been neglected in most previous work in this field. Evidence is presented which indicates that the immediate effect of x-ray treatment is to increase the supply of nucleic acid but at the same time to upset its organization, thereby increasing the nucleic acid "charge" unabsorbed on the chromosomes, thus producing the sticky effect which interferes with spiralization and other chromatid functions. This excess nucleic acid is carried away at a rate proportional to cell activity. "Cold starvation" apparently does not involve an actual deficiency of nucleic acid in the cell but merely the incapacity of nucleic acid to enter the nucleus and be transformed from the ribose to the desoxyribose form. The breakability of a chromosome is dependent not on its size but on its nucleic acid charge; that is, the nucleic acid sticking to its surface. Chromosomes with a nucleic acid charge are either unbreakable by x-ray or, what amounts to the same thing, capable of very prompt reunion. Recognition of the varying nucleic acid charge on euchromatin and heterochromatin during the mitotic

cycle and under experimental conditions is believed to be essential to an adequate interpretation of x-rays effect. These effects are directly upon both cytoplasm and nucleus, and indirectly upon each through the other.

That heterochromatin is broken but little in cells of *Trillium* while it is broken readily in the sperm of *Drosophila* is believed by these authors to be due respectively to a presumed charged and an uncharged condition of the chromosomes. Muller (45), however, on the basis of further work on *Drosophila* again warns that what is called heterochromatin in mitotic chromosomes and in salivary chromosomes is for the most part not the same thing and that, especially in studies of breakability, it is misleading to apply the name "heterochromatin" to both.

Whiting (46, 47) believes that the high sensitivity to x-ray at metaphase and anaphase stages in *Habrobrachon* argues strongly for dependence of the ionizing effect upon the tension that the chromosomes are under at that time. She too finds that if a single chromatid is broken the fragments remain attached to their uninjured partner and reappear in division II. A further interesting observation is that "lethal" dosages are not lethal to the cells immediately affected but only to their descendants. Fragmentation in itself is not lethal, but loss of fragments is. The adhesion of ends of nonhomologous chromosomes has been studied in *Drosophila* by Hinton (48) who finds that these adhesions are influenced somewhat by temperature and very little by the cytoplasm; but these adhesions are definitely not random, and represent potentialities of chromosomal ends which are usually not realized. When they are pulled apart by microdissection they never lose or gain a band. Darlington & La Cour maintain that healing of broken ends, like chromosome breakage phenomena in general, is a function of nucleic acid charge, and that the distinction in this respect is not between telomere (Muller) and intramere, but between ends charged or uncharged with nucleic acid.

Some work has been done on the mechanism of chromosomal movements. Corman (49) believes evidence has now accumulated to justify the inference that chromosomes move during anaphase through the agency of a traction fiber which the chromosome organizes or selects, and itself causes to contract. McKnight & Cooper (50) find that contrary to earlier opinion, chromosomes

$X^1$  and  $X^2$  in *Drosophila miranda* actually synapse with the Y chromosome and consequently, while the "directed" segregation of  $X^1$  and  $X^2$  always to the same pole is still unexplained, it may not prove quite so puzzling in the end as it at first appeared. It is possibly somewhat in line with more or less similar segregation that may occur in *Oenothera*, *Datura*, and *Himulus*.

Another form of preferential segregation is revealed by the knob-bearing chromosomes in maize, where distribution of the different partners can be determined by inspection. On cytological grounds Longley (51) agrees with Rhoades that in megaspore formation a preferential segregation does occur, and he finds it especially apparent in pair 10. If known genes happen to be located near one of the knobs this differential segregation may be further revealed by deviations in phenotypic ratios. When two nonhomologous chromosomes are both involved in this type of segregation there may be an appearance of "false linkage," which has nothing to do with linkage in the ordinary sense.

One of the most extraordinary of the current findings is reported in Shrader's papers (52, 53) on bugs of the genera *Loxa* and *Mayrinia*. In these insects the testes are divided into several lobes in which spermatogenesis is of the usual type in all except the fifth. In this lobe, only, stages beyond the apparently normal spermatogonia show fusion of cytoplasm, migration and constriction of nuclei, and formation of amorphous giant-cell masses which finally break up and divide fairly evenly, but with the first metaphase plate showing anywhere from two to two hundred dividing chromosomes. A second division follows and the resulting spermatids and spermatozoa differ enormously in size and chromosomal content. Whether or not these bizarre spermatozoa are functional is unknown.

*Rejuvenescence and hybrid vigor.*—A still puzzling problem of chromosomal relations is the seemingly different overall effect that is produced by the union in the zygote of two more closely, or less closely, related sets of chromosomes. From time immemorial it has been commonly believed that there is some inherent physiological disadvantage from close inbreeding and at least a temporary advantage from cross-breeding. On the whole this popular notion has been borne out in most cases by scientific tests, although there are forms such as the rat and mouse where it has not been shown that prolonged inbreeding has any deleterious effects

whatever. The kind of advantage that may arise from cross-breeding and heterosis is illustrated by the currently popular "hybrid corn," and perhaps presently by somewhat similarly synthesized "hybrid tomatoes" (54). In many cases heterosis seems to involve something more than the mere combination of favorable dominants and the suppression of undesirable recessives. In his review of the subject Whaley (55) expresses the opinion that "any attempt to arrive at a simple definitive explanation of the genetic basis for the phenomenon of hybrid vigor seems unwarranted by the evidence at hand." It is perhaps possible that the problem is to some degree a cytoplasmic one.

It has been suspected in some quarters that in many plants, hybrid vigor instead of being an index of general physiological efficiency, is merely the result of a favorable initial start, perhaps in some way related to embryo-endosperm relations. Buchholz (56) finds such is not the case in pines where the firmly encased seed has already reached full size before fertilization takes place, thus definitely limiting the possible final development of the embryo. A further point favorable to these studies is that all the flowers of a given tree are fertilized within a period that has a range of not more than  $\pm 2$  days, enabling one to know the age of successive stages with considerable accuracy. In a cross between *Pinus murryana* and *P. banksiana* the hybrid embryos were found to grow much faster than those of either parent but, because of the above-mentioned limitations, were no larger in the ripe seeds. Hybrid vigor again showed itself in the young trees, indicating that some kind of general growth efficiency is involved. Buchholz concludes that "hybrid vigor is nothing that can be detected by a morphological study of the embryos themselves. The nature of hybrid vigor is, however, definitely a physiological vigor of growth; its real explanation is to be sought in physiological, possibly biochemical investigations."

Probably closely related to the question of heterosis is that of rejuvenescence, and, in turn, senescence. Here again both nuclear and cytoplasmic factors seem to be involved in the phenomena. Protozoa have long seemed favorable subjects for study of the problem, one point of view being indicated by the familiar aphorism that unicellular organisms are potentially immortal, which opinion seems to imply that periodic reconstitution of the germ-plasm is quite unnecessary in such forms. In a long series of pains-

taking investigations, Jennings (57) has studied various aspects of the problem in *Paramecium*. He uses the term inbreeding when clones derived from two ex-conjugants are mated, and self-fertilization when conjugation occurs within a single clone. The former greatly increases the mortality among exconjugants while the latter does not do so, possibly because the nuclear material is different in the one case and not in the other, but the solution still appears by no means simple.

In further studies of the subject Jennings (58) is led to the conclusion that death is not a by-product of animals having become multicellular but that it is a phenomenon of wide occurrence among protozoa as well as metazoa and results from conditions intrinsic to the organism. Most clones he finds ultimately decline and die out if they do not undergo some form of sexual reproduction. Nevertheless, this reproduction itself takes a heavy toll, for in addition to some rejuvenated strains, conjugation produces vast numbers of weak, pathological, and abnormal clones whose fate is early death. The rejuvenating function of conjugation, Jennings concludes, is distinct from, and in addition to, its function in producing variability through redistribution of genes. The nature of rejuvenescence itself is "one of the ultimate brute facts of nature," still quite unexplained. Among all the clones, most of them destined to early death, are some which show such vigor that they seem capable of multiplying vegetatively for an indefinite period (although many supposedly so, are not). It is only in such rare clones that "immortality" of protozoa in vegetative reproduction is achieved, if it is ever achieved at all.

*Speciation.*—While most cytological studies are primarily directed toward a better understanding of the structure and behavior of chromosomes, many of them throw considerable light on the question of speciation, which has come to be regarded as in no small degree a physiological problem. One of the important aspects concerns the determination of available chromosomal and genic diversity in natural populations. Among a few representative wild species, Spurway (59) records twenty-one new mutants in *Drosophila subobscura*; Stalker (60) reports fifty-two new mutant genes in *Scaptomyza graminium*; and Ives (61) finds an average incidence of .598 lethal or deleterious genes for every chromosome II in wild eastern populations of *Drosophila melanogaster*. The latter author points out that this incidence is so great that almost

no individual homozygous for any one particular autosome has a survival expectancy as great as that of the average heterozygote, and that the maintenance of this species must therefore be largely dependent on "heterosis." The situation seems to have come about through the establishment of large interbreeding populations concomitantly with development of widespread commercial fruit growing. It is suggested that this phenomenon may well tend to slow down evolutionary progress and might even lead to racial degeneration if a vigorous competitor were to appear.

In the foxes of Canada, according to Butler (62), recessive genes are showing quite a different trend. It appears that two main genes, *A* and *B*, are chiefly involved in determination of coat color in these animals. One of the recessives *a* (responsible for a silver pattern) has its highest incidence in Alaska, while a gene with a similar effect, *b*, is most abundant in Quebec. The incidence of *B* falls from almost 1.0 in British Columbia to 0.82 in Quebec and over the same range *A* rises from 0.73 to 0.90. Long range records based on pelts obtained by the Hudson's Bay Co. show that both *a* and *b* are slowly declining in incidence.

Such changes as occur in the constitutions of populations are no doubt primarily genic in origin, but the isolating and selective mechanisms that potentiate these changes are obviously varied. Among these, polyploidy still holds an important place in botanical discussions, but a noticeably large number of current reports emphasize the aberrancy and instability of many polyploid forms [Cooper & Brink (63), Meyers (64), Rich (65)]. In this connection two rubber-producing plants have proved of some theoretical as well as practical interest. In the Russian dandelion, *Taraxacum koksaghyz*, Warmke (66) found that tetraploidy induced by colchicine resulted in plants that on the average produced three, or even four, times as much rubber as the corresponding diploids. In guayule, Esau (67) and others find that achenes from non-pollinated 36-chromosome plants contain no embryos, while those from nonpollinated 72-chromosome plants do, but in the latter endosperm development is defective. The situation is still further complicated according to Rollins (68, 69) not only by a long series of polyploids but by frequent crosses with a related species *Parthenium incanum*, giving chromosome numbers that run through the range 36, 54, 63, 72, 81, 90, 99, and 108. Somatically there is an almost complete transition from one species to the other.

Powers (70) thinks that in *Parthenium* there is convincing evidence of a close relation between apomixis and polyploidy, and postulates three steps in the evolution of apomixis in such stocks: (a) failure of reduction in number of chromosomes, (b) failure of fertilization, (c) regular development of unreduced, unfertilized eggs. It would seem, however, that there might be some residual problem with reference to the role of the endosperm.

That changes in chromosome number, and the attendant changes in chromosome structure, have played an important role in creating isolation between groups and among individuals within species is emphasized by Babcock (71), who nevertheless doubts the origin of new species by sudden profound changes. Polyploidy and changes in chromosome number he believes have not been important in creating morphological and physiological differences between species, these being due to accumulation of the genic changes which they favor. An important review paper that should be mentioned at this point is that of Little (72) on "Gene segregation in autotetraploids."

One other isolating mechanism of possible importance is dependent on sexual selection. In a number of different species Dobzhansky and collaborators (73, 74) have tested the extent to which males prefer females from their own or some remote region, e.g., Mexico or Brazil. The results are not all consistent but the evidence seems clear enough that there are preferences and that, in general, discrimination is against "foreign" females. Mayr & Dobzhansky (75), using *Drosophila pseudoobscura* and *D. persimilis* which are extremely similar checked the effect of enforced association throughout life. Fertilized females of the two species were put in the same culture bottles and allowed to deposit eggs after which they were removed and the young permitted to grow up together in the same medium. Adult flies were taken out immediately after emergence and so mated that in each bottle there would be ten males of one species, ten females of the same species and ten of the other species. After an appropriate length of time, dissection of the seminal receptacles of all the females showed that cross-breeding had been no more frequent than under usual conditions. Study of a number of other factors failed to reveal the real basis for discrimination, except that while at ordinary temperatures *D. persimilis* males showed a clear preference for their own kind, at 18° their reaction was apparently reversed and they



preferred *D. pseudoobscura* females. Although in these species there was no evidence that vision plays a role in selective mating, Rendel (76) did find evidence that it does so in *D. subobscura*, where eyeless and white-eyed males do not breed normally.

*Sex.*—In the manifestation of sex, genic and endocrine effects are often interrelated and interdependent, but in insects this handicap seems to be little evident. Sturtevant (77) finds a gene in chromosome III of *Drosophila* which, except for a few minor details, almost completely converts genetic females into males. Hays (78) finds the primary sex ratio in chicks from different individual hens to range from twenty-two to sixty-five males to each fifty females and suspects the existence of some segregating autosomal sex determinants. In Hymenoptera, Flanders (79) believes that the occasional production of uniparental females is the result of doubling of chromosomes in the primary oogonia, and Heidenthal (80) finds the sex ratio a useful index of the effect of x-ray treatment on sperm in *Habrobrachon* males.

In Amphibia, Fankhouser (81) notes evidence that polyploidy has little effect on size and that the female is probably the heterozygous sex, while Spurway (82) thinks that in two species of *Triton* the females are probably homozygous. She suggests, however, that, as in *Lebistes*, the sex-determining mechanism may not be the same in all the species. Humphrey (83) presents convincing evidence for *Amblystoma tigrinum* and *Siredon mexicanum*, where genetic females converted to functional males by testicular hormones and mated to normal females produced 509 male and 1,588 female young, which is close to expectation on the assumption that the normal female is heterozygous.

Some attention has been given to hermaphroditic forms. Purdy (84) finds that hermaphroditic *Tuberfex* worms isolated soon after birth and raised to maturity in filtered water are apparently able to effect self-fertilization and produce numerous young. In case of hermaphroditic goats, which are common, Eaton (85) finds that probably two linked genes are involved, one of them an allele of *P* (polled). The hermaphrodite-gene is effective in the female genotype, but not in the male. The sex ratio of goats, as recorded is notoriously high, but Eaton finds that if all intersexes are counted as genetic females, the ratio falls to approximately 103 males to 100 females.

*Embryology.*—A considerable number of new genes which



make their presence manifest in the embryo continue to be reported. Amundson (86) describes a twentieth lethal in the chick which induces a number of anomalies including a crooked neck and a short upper jaw making it impossible for the embryo to break its way out of the shell. Sturkie (87), who had previously found that the incidence of polydactyly in heterozygous fowls could be significantly lessened by lowering the temperature at critical periods during incubation, now finds that he is unable to produce comparable results with other traits of similar penetrance. According to Bauman (88) genes for polydactyly are more effective in the feet than in the wings, on the left side than on the right. Landauer (89) finds that the life of chicks homozygous for the lethal *CpCp* can be prolonged by proper adjustment of temperature early in incubation. The control of rumplessness has also been further studied by Landauer and his students (90). Shaking normal eggs before incubation, injecting them with insulin, incising the backs of young embryos (Zwilling, 91) are among the things which cause appreciable numbers of genetically normal chicks to develop into rumpless phenotypes. It becomes increasingly apparent that this trait, like some others involving developmental failure, may be induced by either dominant or recessive genes and likewise by a diversity of extragenic disturbances occurring before some, as yet undetermined, period of embryonic life has been reached.

Two more types of disharmonious development of the jaw with consequent disabilities have been described, one in dogs by Phillips (92) and one in Rambouillet sheep by Nordby *et al.* (93). In both, a number of recessive genes, or complicated modifiers, seems to be involved. Barnicot (94) finds that in mice the "Gray lethal" shows a greatly reduced bone absorption throughout the skeleton and tolerates injections of parathyroid hormone in amounts several times that which would be fatal to mice with the normal allele. A study which incidentally throws much light on normal development is reported by Bryson (95) in which he shows that screw-tailed *CHS* Bagg albinos have a broad, unsegmented sternum purely as a secondary effect of a gene which reduces the size of the ribs so that they fail to make contact with the sternum which therefore develops abnormally. Gluecksohn-Schoenheimer & Dunn (96, 97, 98) discuss in some detail the genetic background for sirens, aprosopi, and intestinal anomalies in mice. The ultimate, seemingly unrelated, effects of the *Sd* gene on tail and uro-

genital system they think must be far removed from its initial primary effect. Like Fisher & Holt (99) they have introduced the gene into several different strains and revealed the presence of numerous modifying factors, but on carrying the analysis further, they find that in one strain this gene may be more dominant in one of its effects and less so in the other, while in a different strain the reverse may be true. Whether the problem here is fundamentally different from that mentioned in the opening paragraphs of this review is doubtful.

*Genetic differences in the reactions of adult animals.*—Demarcations between what is embryological, juvenile, or adult are for the most part indistinct. Silberberg & Silberberg (100) find that in mice, where regressive changes in epiphysial cartilages are under the influence of complex interacting endocrine and genetic factors, the slowly ageing strains *C57* and *CBA* show a greater difference between the sexes than do the more rapidly ageing *A<sub>1</sub>C<sub>3</sub>H* and *D*. Following early gonadectomy, carcinomata of the suprarenal were found frequently by Wooley & Little (101) in mice of the *JAX ce* strain, but not at all in *dba* and others. In various crosses involving genes for high and low incidence of leukemia, Kirschbaum (102) finds that the most striking feature is a delayed time of onset, which he thinks may be attributable to hybrid vigor. Kirschbaum & Bittner (103) find that while susceptibility to induced cancer is strain-specific, it is not necessarily correlated with a tendency to spontaneous cancer. Dmochowski (104), using *C57*, *Strong A*, and other strains, and employing a technique for desiccating tumor tissue over phosphorus pentoxide in a vacuum and then injecting it in small amounts, finds that tissues treated in this way can induce carcinomata in strains of entirely different genotype from those in which the tumor first appeared. Strong (105) finds the protoporphyrin content of the Harderian glands in mice to show a parallelism with cancer susceptibility, and to follow the female parent more closely than the male. The histopathology of the nervous system in the ataxic rabbits described earlier by Sawin, Anders & Johnson, has now been studied in detail by Anders (106). The disease, which appears only in homozygous animals, presents a very consistent syndrome. Its onset occurs at about the seventy-third day of life, at which time the animal begins to show a staggering gait, followed in the next few days by increasing tremors, frequently lateral nystagmus, hypersensitivity to sound, a gradual

fall in temperature, and finally complete prostration and death. No gross anomalies in either the nervous or muscular systems are apparent, but Marchi and Bodian preparations from the brain show progressive degenerative lesions in nuclei and tracts, the nature and sequence of which are such as would have led one to expect the clinical symptoms as observed. One wonders whether in this and more or less similar cases in man we are dealing with mutations that profoundly change the intrinsic function of certain cells, or ones that merely lay them open to attack by some subtle virus or other extraneous agent.

The role of hereditary factors in many serological phenomena is now well recognized but some aspects of the field still appear to require much further exploration. Cushing's current studies (107) on complement in a variety of species emphasize that reactions are influenced by the kind (species) of complement as well as by the antigens and antibodies involved. In further studies with Muscovy and Mallard ducks, McGibbon (108) finds that the two substances which at first appeared to be specific to the Muscovy can now each be broken up into several components. From hybridization experiments with ringneck and pearl doves, Irwin & Cumley (109) are led to believe that there may be several duplicate genes in different chromosomes. On the other hand, Owen, Stormont & Irwin (110) find that of the thirty antigens identified in cattle and previously thought to be controlled by separate individual genes, many are products of multiple alleles or closely linked genes, so that it may turn out that the number of loci involved is smaller than previously supposed. The situation in man is not yet clear either, especially with reference to the *Rh* series. At the moment it appears [Wiener *et al.* (111)] that there may be eight alleles in this series and that in various combinations these can produce twenty-one different types (phenotypically  $Rh''rh'' = RH''rh$ , etc.). The revealed frequency of multiple allelism among genes affecting serological reactions might not have been predicted in advance and may have unsuspected significance. A sole case of linkage of a blood group with an unrelated trait is reported by Sawin *et al.* (112) who find that in the rabbit the gene for *A* antigen is linked with that for brachydactyly.

As for racial distribution of genes, Owen *et al.* (110) tested thirty cellular antigens in 569 Guernsey and 513 Holstein-Friesian cattle and found that no single antigen was peculiar to either breed,

but eighteen of them were significantly more frequent in Guernseys and five in Holsteins. Wiener & Wade (113) found that nine chimpanzees out of ten were of group *A* and the other one group *O*; none of fifteen had the *Rh* factor. With various collaborators Wiener (114, 115) has studied racial distributions of human blood types in New York City. Among the Chinese, *Rh*-negative individuals are rare, and all *A* and *AB* individuals have the gene  $A_1$ .

The incidence of *M* and *N* is as in whites. Negroes differ from whites much more in the incidence of genes in the *Rh* series than in the *M-N* or *O-A-B* series, the greatest difference being in  $RH_0$ , which is about ten times as frequent in the Negro as in the white.

Of the many primarily anthropological papers of genetic and physiological interest only one will be mentioned briefly, that of Lasker (116) in which the author reports evidence of a wide range in degrees of plasticity even in different aspects of the teeth. Dental caries is so subject to environmental influences that no racial trend could be detected in its manifestation, while the shape of the upper incisors is so strongly genetic as to show distinctive differences between the various regions of the country. The question of differences in various other, especially mental, traits is a matter of genetic interest which should not be entirely ignored in this review. Certain aspects of the matter are touched upon in articles by Garrett (117), Montagu (118), Herskovits (119), Strandskov (120), Dobzhansky (121, 122), and in a little book by Rife (123), but unfortunately studies in this section of the subject are so often hampered by biases, now in one direction now in another, that sound progress in some aspects of human genetics seems to be threatened for a long time to come.

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## DEVELOPMENTAL PHYSIOLOGY<sup>1</sup>

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Because of the background and primary interests of the author as well as the limitations of space, this review will be largely devoted to a presentation of the recent additions to our understanding of the development of the mammalian embryo and fetus. The field is one of exceptional breadth and considerable activity for it has stimulated interest in many branches of animal biology. Contributing to it are the classical embryologist and anatomist interested primarily in problems of morphogenesis; the physiologist and zoologist investigating the development of function; the biochemist concerned with chemical differentiation and the chemical differences which exist between typical and atypical cellular growth; the obstetrician and pediatrician who add a clinical interest to problems of fetal nutrition and of fetal anomalies. It will be apparent that these various points of view are interdependent and that a presentation of progress in developmental physiology must include the advances made in its closely related fields of interest.

Several books, which do much to integrate the knowledge in the subject, have appeared. *Human Embryology. Prenatal Development of Form and Function* by Hamilton, Boyd & Mossman (1) is a presentation of human embryology in the light of the advances of the past twenty years with emphasis upon a correlation of the development of form and function. Barclay, Franklin & Prichard (2) have published a volume on *The Fetal Circulation and Cardiovascular System, and the Changes that They Undergo at Birth*. Corner (3) in *Ourselfs Unborn* has discussed problems of the early embryo, teratology, and the contribution of embryology to the evaluation of man's place in nature. Gesell & Amatruda (4) have written *The Embryology of Behavior: The Beginnings of the Human Mind*.

*Human embryology*.—Valuable additions have been made to the understanding of early stages of the human embryo. The *in vitro* fertilization of human ova has for the first time for any of the higher animals been reported by Rock & Menkin (5). They ob-

<sup>1</sup> This review covers the period from January, 1944 to June, 1945.

served two eggs in the two-cell stage, 40.5 and 45 hours respectively following contact with spermatozoa. Two eggs were seen in the three-cell stage 46 hours after exposure to spermatozoa; the findings in this respect are in general agreement with those reported by Lewis & Hartman (6) on the monkey egg fertilized *in vivo* and cultured *in vitro*. A series of five previllous and two villous normal human ova ranging from 7.5 to 16.5 days in developmental age has been described by Hertig & Rock (7). The specimens show that the human blastocyst implants on the posterior wall of the uterus, probably during the late sixth or early seventh day of its development, on endometrium that may range from the eighteenth to the twenty-third day of its development. The solid syncytiotrophoblast of the early implanted blastocyst develops lacunae, beginning on the eighth day, which subsequently coalesce and begin to receive maternal blood on about the eleventh day. Chorionic villi form from peripherally growing masses of cytotrophoblast which arise from the chorionic membrane on about the twelfth day. The peripheral syncytiotrophoblastic shell of the previllous ovum is "desquamated" at approximately the same time that the cytotrophoblast of primitive villi makes contact with the decidua. The same authors have more recently obtained two more normal human ova, one not over 7.5 days of age (8), the other approximately 9 to 10 days of age (9). Davies (10) and Hamilton, Dodds & Barnes (11) have also described normal human ova ranging in estimated age from 9 to 10.5 days. A persomite human embryo with chorda canal and prochordal plate and of ovulation age estimated to be 18 or 19 days has been described by George (12).

The age of early human embryos is often uncertain and, because size is an unreliable criterion, the investigator is forced to depend upon the apparent state of development if he wishes to gauge the status of an embryo. To meet this end, Streeter has planned to set up a practical standard of comparison for human embryos from the earliest available up to fetuses of about the eighth week after ovulation. He has presented his age-group XI, 13 to 20 somites, and age-group XII, 21 to 29 somites (13). Photographs and diagrams of representative embryos of the particular stage are given together with descriptions of the external form and internal structure. The work is accompanied by tables which list the embryos of each group in the Carnegie Collection as well as those elsewhere which have been described in the literature. Clat-

worthy & Anderson (14) have taken data from the literature on human development and for a number of organs have prepared charts which show the rate of growth of a given organ relative to the rate of growth of the whole fetus at various fetal ages. The weight of the organ has also been plotted against fetal age.

*Skeleton and musculature.*—To test the view that in very early postnatal life animals in absence of the thyroid cannot respond to pituitary growth hormone, Scow & Marx (15) treated rats completely thyroidectomized at birth with a purified preparation of growth hormone. They noted that skeletal size then increased at an accelerated rate but no acceleration was observed in the appearance of secondary ossification centers. Scow & Simpson (16) studied the effect of thyroidectomy in the newborn rat and among other effects noted an exceedingly slow but continuous increase in size of skeleton with delay in appearance of secondary ossification centers. Noback (17) has written on the developmental anatomy of the human osseous skeleton during the embryonic, fetal, and circumnatal periods, and Giblin & Alley (18) have reported on studies of the growth of the skull. Latimer (19), continuing his observations on the prenatal growth of the cat, has measured the weight of the musculature relative to body weight during prenatal development and compared changes in this ratio to that characteristic of the adult.

*Abdominal viscera.*—An investigation of the origin and differentiation of the alpha and beta cells in the pancreatic islets of the rat has been undertaken by Hard (20) with the purpose of determining, by cytological methods, the extent to which the islet cells appear capable of secretory activity during intrauterine and early postnatal development. In the embryonic and early postnatal stages of development, islets originate from three and possibly four sources as distinguished by their relationship to the developing duct system. The beta cell is the only islet type to differentiate before birth. Beta granules were first distinguished during the nineteenth day of gestation and the cytological evidence indicates that secretory activity begins in the beta cell at or about the time of birth. Alpha cells were first recognized during the second day of postnatal life and some appeared to be actively secreting three days later.

Hard, Reynolds & Winbury (21) have reported that glycogenic activity first appears in the liver of the fetal guinea pig at a gesta-

tion age of 50 to 55 days and that glucose in the maternal portion of the placenta decreases during the last quarter of pregnancy as glycogen rises in the fetal liver. During this period, the quantity of fat in the fetal liver rises but at birth there is both marked glycogenolysis and reduction of liver fat. Deane (22) has presented a cytological study of storage and secretion in the developing liver of the mouse from birth to 45 days. Glycogen is present in the hepatic cells at birth and increases up to the 18th day. Secretion of bile acids appears to begin during the first week of postnatal life and to increase with age. Sharples (23) has described the histogenesis of the argentaffin cells in the stomach and duodenum of the rat and Andrew (24, 25) has reported on age changes in the spleens of rats and man.

*Urogenital system.*—The origin and differentiation of the epithelium of the urogenital sinus in the opossum as well as the modifications induced by estrogens has been studied by Burns (26). The lining of the urogenital sinus reacts sharply to estrogenic hormones by assuming a characteristic histological structure similar to the vaginal epithelium of the adult female and thus can be marked long before it would normally respond to hormone produced in the animal's own ovaries. The extent to which the sinus epithelium participates in the formation of later stages of the urogenital organs (neck and trigone of the bladder, sinus horn, and vagina) is consequently readily followed. The results suggest that stratified squamous epithelium found in the vagina, urethra, and prostatic utricle of higher forms and under experimental or pathological conditions in the bladder and even the uterus in all probability is derived from sinus epithelium and reaches its relatively wide distribution in the adult by spreading from the sinus region rather than by local differentiation *in situ*. Hartley (27) has studied the effect of sex hormones on the development of the urogenital system in the garter snake. Androgens injected into the amniotic cavity during the first month of gestation stimulate spermatogonial mitoses and growth of seminal tubules in the testis; in the ovary they inhibit the development of follicles and cause persistence of germ cells and sex cords in the medulla. Estrogens cause an increase in stromal tissue and a decrease in size of the seminal tubules of the testis but do not affect the ovary. Hypertrophy of the müllerian duct of the female follows injection of either androgens or estrogens during the last month of gestation. Rubin (28) has examined in the opos-

sum the relation of hormones to the development of Cowper's gland anlage in the male and of its homologue, Bartholin's gland anlage, in the female. A comprehensive account is given of the normal development of these glands. Androgens and estrogens have been found to exert a similar effect on the early primordia of the glands; they produce a general stimulation of growth and precocious canalization of the cords. The effect of gonadotropic hormones is also discussed. Pouch-young male opossums, castrated at an early age, were found to have normal Cowper's glands up to the latest age studied; this result indicates that hormones of the testis are not essential for the normal morphological differentiation of the glands. Nelsen (29) has described the development in the opossum of genital rudiment, genital ridge, and primary sex cords. Sex differentiation was found to have occurred in all animals by the end of the first week following birth.

The testes of a series of thirty bulls, ranging in age from one month to fifteen years, were examined microscopically by Hooker (30) with the aim of correlating changes in the testicular cells with changes in androgen content. Changes in the size and structures of the tubules are not associated with changes in androgen level. The large increase in androgen content occurring after two years of age is accompanied by alterations of a comparable degree in vacuolation and to a lesser degree in numbers of Leydig cells and it is concluded that the cytological change most conspicuously correlated with change of androgen content is vacuolation of the Leydig cells. The development of the testis in the pheasant has been reported on by Kirkpatrick & Andrews (31).

A review of the embryology of the human prostate has been given by Swyer (32). He found histological evidence at time of birth of stimulation of the gland by maternal estrogens present in the fetus; this persists for six or seven weeks after birth. Little differentiation or increase in size was noted up to the ninth year. At puberty, under the influence of the male hormone, which then begins to be secreted in effective amounts by the testis, the prostate begins to grow rapidly and within six months to one year has become transformed into the adult type of organ.

The development of glomeruli in the human kidney has been studied as a function of fetal size and gestation age by Potter & Thierstein (33). Cessation of the production of new glomeruli has been found to be primarily dependent on fetal size and only second-

arily on gestation age. Anatomical maturity of the fetal kidney, compatible with normal adjustments to extrauterine life, appears usually to be attained at least one month prior to the end of a normal pregnancy. The authors suggest that the status of glomerular production constitutes an index of the maturity of the fetus. MacNider (34) has observed the occurrence of stainable lipid material in the renal epithelium of dogs of various age groups. Microscopically demonstrable lipid is not present in the cells of the proximal convolution in puppies but makes its appearance and increases in amount as the animal ages. The development of the mesonephros in a teleostean fish has been described by Moghe (35).

*Nervous system.*—An investigation of chemical changes which may take place in induced neural structures has been undertaken by Boell & Shen (36). They have found that the cholinesterase activity of secondary, induced neural structures in *Amblystoma punctatum* is of the same order as that of the primary neural tissues of the host and much greater than that of ectoderm which did not receive the stimulus of induction. They conclude that induction, in addition to causing the development of distinct morphological changes, also apparently stimulates the development of the biochemical attributes characteristic of normal nervous tissue.

The differentiation of the muscle fiber in human fetuses and developmental stages of the motor end plates have been described by Cuajunco (37) who has correlated his findings with observations on human fetal behavior. In several specimens of his series, he obtained evidence of possible plurisegmental innervation from the presence in a single muscle fiber of several end plates connected to different nerve fibers, or of a single plate receiving the terminations of more than one nerve fiber. The evidence indicates that spontaneous fetal movements may begin prior to the union of muscle and nerve. Muscle fibers, at the time the nerves have reached them, have acquired abundant myofibrils with distinct striations. Stronger "quickening" movements appear to be possible in the sixteenth week for in this stage the nerve endings are in a relatively high state of development and the muscle fibers are similar to those of the adult in the arrangement of sarcostyles and nuclei.

An experimental study of factors influencing the course of nerve fibers in the embryonic central nervous system has been undertaken on the chick by Rhines & Windle (38). The authors

review the theories which have been proposed. The mechanical theory emphasizes the arrangement of the ground substance and assumes that nerve fibers follow available paths in it. The chemotropic theory supposes that particular groups of nerve fibers are attracted to specific regions because of their chemical characteristics. The theory of galvanotropism (neurobiotaxis) suggests that differences of electrical potential between regions cause axons to grow with the current and dendrites to grow against it. A theory of stimulo-genous fibrillation in embryos, in support of the theory of neurobiotaxis, claims that the descending medial longitudinal fascicle initiates development of the cranial motor nuclei, causing the first axonal processes of neighboring neuroblasts to grow away at right angles from this tract. The authors studied the effect of surgical removal of portions of the brain upon the development and course of central fiber tracts in chick embryos. No relationship was found between the presence of the diencephalic components of the medial longitudinal fascicle or any other longitudinal tract and the longitudinal course taken by commissural fibers after crossing the midline. Development of cranial motor nuclei was observed in the absence of all longitudinal tracts. Rhines & Windle conclude that their experiments do not appear to support the theories of neurobiotaxis and stimulo-genous fibrillation but favor the view that orientation and structure of the substrate are important factors in directing the growth of new nerve fibers in the central nervous system.

An investigation by Hall & Schneiderhan (39) on spinal ganglion hypoplasia after limb amputation in the rat extends to mammals observations on the relationship of the development of the spinal ganglion to its peripheral field. The fore limbs of fetal rats were amputated from the fifth to the seventh day before birth, the animals carried to term and then studied. Hypoplastic defects were found in nearly all the ganglia of the operated part, the diminution in cell number closely approximating that in volume. Decreases in cell number and in cell volume each amounting to almost 80 per cent were observed. That the effects were not due to ascending degeneration was indicated by the absence of cytological changes characteristic of such degeneration.

Piatt (40) performed extirpation and isolation experiments on embryos of *Amblystoma punctatum* to test the generally accepted thesis that the cells of the nucleus of the fifth cranial nerve



are derived from neural crest. The experimental results are consistent with this view. The data did not, however, preclude the possibility that these cells might arise from additional sources and Piatt believes it probable that neuroblasts of the presumptive alar plate contribute to the mesencephalic V root nucleus. Hogg (41) has studied the embryological development of the commissura posterior in the human spinal cord and Pearson (42) has made observations on the roots of the facial nerve in human fetuses. Gruenwald (43) has described disintegrative changes in the embryonic brain of man and chick which frequently lead to the formation of conspicuous cysts in various derivatives of the fore-brain. All these changes subsequently disappear completely during normal development. The histogenesis of the neurohypophysis of the pig and of pituicytes in the chick have been studied by Shanklin (44, 45). In the pig, differentiation of cells in the ependymal layer begins between the 10 and 15 mm. stages and there is a fairly large infundibular process in the 60 mm. stage. In fetuses of 125 mm. (about halfway through gestation) pituicytes acquire vascular processes and foot plates.

The oxygen environment of the brains of postmature rabbit fetuses, obtained by the injection into the mother of chorionic gonadotrophin and progesterone on the twenty-fifth day of pregnancy, has been studied by Barcroft & Young (46). The oxygen saturation of the blood in the posterior fontanelle falls after the twenty-fourth day and by the thirty-fifth day is on the average only 17 per cent saturated. The authors suggest that the active intrauterine respiratory movements noted during the period of postmaturity can be attributed to anoxia and that the ultimate death of the fetuses is due to asphyxia.

Windle (47) has discussed the changes which may take place in the brain following asphyxia and points out that asphyxia preceding or accompanying birth is an important hazard both with respect to the life of the human infant and to damage of its central nervous system. The fetus and newborn animal are more resistant to deficiencies of oxygen and hence they survive longer than the adult in the presence of an inadequate supply of oxygen. In experiments on guinea pigs, made anoxic by occlusion of the umbilical cord, brain damage was found to parallel approximately the duration of anoxia. All animals whose placental circulation was interrupted only until respiratory efforts had become weak and



which required little or no resuscitation, usually showed indefinite or only slight changes. Those animals whose placental circulation was occluded for eight minutes or more, requiring more than five minutes to resuscitate, showed definite to marked changes. The neurological symptoms usually did not persist in marked form throughout life, and were often only transient. Preston (48) has analyzed the late behavioral aspects of anoxia which occurred in a series of 132 children before birth, at time of birth, or after birth. The anoxia was found to have damaged the central nervous system of every child seriously enough to affect his subsequent behavior. Lesser degrees of anoxia appeared to cause abnormal, hyperactive behavior; greater degrees were followed by apathetic behavior, loss of intelligence, and in some instances epilepsy. Arrest of physical, mental, nervous, and emotional development was evident throughout the series. At least partial recovery of normal function took place in the untreated child between the ages of five and twelve.

During asphyxia, tissues must depend upon glycolysis for energy and for their survival. It appears that the central nervous system is not equally susceptible to anoxia in all its parts and that susceptibility is a function of age. For these reasons, Chesler & Himwich (49) were interested in measuring the glycolytic rate of various parts of the central nervous system during growth and development. Cats and dogs were studied. In the newborn, glycolysis was found to be most rapid in the medulla and to be lower both above and below this region. In the adult, the highest rates were observed in the caudate nucleus and cerebral cortex while lower rates were found at lower levels. Glycolysis of the medulla and cord decreases progressively with age; while glycolysis of the brain reaches its peak some time before adulthood and diminishes thereafter. It would be of interest to attempt to correlate these findings with functional and anatomical alterations of the central nervous system produced by anoxia. Sontag (50) has discussed the possibility of modifying fetal behavior, and postulates that the psychophysiological state of the mother influences the behavior pattern of the normal fetus.

*Blood and cardiovascular system.*—Continued interest has been shown in angiogenesis and in the comparison of the elements of the fetal blood with those of the adult. Noback (51) has studied angiogenesis in the amniotic mesoderm of the baboon embryo

about twenty-six days old and concludes that the amniotic mesoderm can have angiogenetic potentialities. The chemical properties of hemoglobin derived respectively from the blood of adult and fetal cows has been compared by Wyman, Rafferty & Ingalls (52) and by Vickery (53). The first group of investigators measured the solubility of fetal and adult carbonylhemoglobins in strong phosphate buffers of ionic strength 4.9 to 5.5 at pH 6.8. They found the carbonylhemoglobins from fetal blood to be more than six times as soluble as that from the adult and consequently concluded that the two hemoglobins are probably different. Vickery's work supports this conclusion. He determined the histidine yielded by samples of crystallized hemoglobin. Adult bovine hemoglobin yielded  $6.81 \pm 0.05$  per cent histidine; fetal bovine hemoglobin yielded  $6.43 \pm 0.04$  per cent histidine, this fact thus showing with a high degree of probability that there is a difference in the amino acid composition of these proteins. In a study of the developmental history of the plasma proteins, Moore, Shen & Alexander (54) obtained data on sera and plasmas from developing chick and pig embryos by electrophoresis, ultracentrifugation, and chemical analysis. By all methods of analysis, the embryonic and fetal plasmas were found to differ widely from those of the adult and electrophoretic analyses showed rapid changes during development.

Mulligan (55) has reported on the blood and bone marrow of newborn puppies; he found, in bone marrow, that erythrocytopoiesis is more active than granulocytopoiesis. Blood formation in relation to diet has been studied in young guinea pigs by Cannon *et al.* (56). Campbell, Brown & Emmett (57) have found that vitamin B<sub>6</sub> is an essential factor for preventing macrocytic anemia, leucopenia, and thrombopenia in young chicks.

Several reports have appeared on the development of the heart and blood vessels. In an investigation of self-differentiation and induction in the heart of *Amblystoma*, Bacon (58) found that explants and gastrocœle implants of heart mesoderm from Stage 11 differentiate into normally curved and chambered hearts with rhythmic pulsations and concludes that complete primary organization occurs early in gastrulation. The results also led to the conclusions that a secondary heart-organizing action is present in the tissue surrounding the final heart position and that heart-organizing activity exists in the endoderm of the archenteron

floor. Romanoff (59), in a study of the heart beat of avian embryos, has found that the rate of the heart changes in almost identical fashion at comparable stages of development in several species of gallinaceous birds. Positive fetal electrocardiograms were obtained in about half of a series of twenty-one gravid women of varying periods of gestation by Paley & Krell (60); positive stethograms were obtained in all but about 20 per cent. Postnatal growth changes in the cardiac ventricles of the albino rat in the first two weeks of postnatal life have been described by Keen (61) and compared with observations on the hearts of human infants. Smith, Pierson & Seitner (62) have reported changes which occur in the media of the aorta and femoral arteries of mice from birth to about 700 days.

The volume of Barclay, Franklin & Prichard (2) presents an historical survey of the subject and the comparative anatomy and physiology of the fetal cardiovascular system. In a review of the book, Windle (63) has summarized statements of the authors' own findings. They found that radiopaque material placed in the superior caval stream passes through the right atrium and right ventricle of the heart without traversing the foramen ovale. A large amount goes through the pulmonary circulation and the remainder is shunted by the ductus arteriosus into the descending aorta. Radiopaque material in the inferior vena cava passes largely through the foramen ovale into the left atrium and from the left ventricle to the arch of the aorta, the coronary vessels, the upper extremities, and the head. A small fraction of the inferior caval stream traverses the right side of the heart, the pulmonary circulation, and ductus arteriosus.

*Placenta.*—The histology and cytology of the placentas of man and monkey have been investigated by means of classical cytological methods and the more recent methods of histochemistry, in an effort to gain insight into the nature of placental function. The outer surface of the syncytium has been found by Wislocki & Bennett (64, 65) to have a variable structure ranging from a brush-like border to one consisting of irregular streamers of cytoplasm; these findings have been taken to indicate an active transfer of fluid and metabolites across the surface of the trophoblast. It is pointed out that the cytology of the syncytium favors the view that it exercises selective and regulatory functions of a complex nature with respect to the passage of substances from

the maternal to the fetal circulation or in the opposite direction. The association in the syncytium of fat droplets and birefringent substances soluble in acetone, and of acetone-soluble substances capable of reacting with phenylhydrazine to form yellow phenylhydrazones suggests that the syncytium is the site of formation of placental steroid hormones. It is also suggested tentatively that the cytotrophoblast rather than the syncytium may be the site of formation of chorionic gonadotropin. Baker, Hook & Severinghaus (66) have presented cytological evidence indicating that the trophoblast of early pregnancy in man performs a significant secretory function, its period of activity corresponding approximately with the time of greatest secretion of gonadotropin. In late pregnancy, reduction in number of mitochondria, lipid droplets, and superficial vacuoles in the syncytium was taken as evidence of reduced secretory activity. No convincing evidence of secretion was found in the decidual cells of the decidua parietalis. Dempsey & Wislocki (67) have investigated the basophilia as demonstrated by affinity for basic dyes and the alkaline phosphatase of the human placenta. Since the cytoplasmic basophilia of the placenta disappears after digestion by crystalline ribonuclease it is concluded that the basic staining is due to the presence of ribose nucleic acids. Nuclear basophilia excepting the nucleolus is not affected by the action of the enzyme. Ribose nucleic acids were found to be inversely related to the activity of alkaline phosphatase; in the course of gestation as the placental phosphatase increases, cytoplasmic basophilia diminishes. The evidence has suggested to the authors a functional interrelationship between placental alkaline phosphatase and ribose nucleic acids. Other evidence is taken to indicate that phosphatase, together with glycogen, is responsible for the deposition of calcium in the placenta. Falkiner (68) has presented certain aspects of the morphology of the human placenta.

The problems of placental transmission have continued to receive considerable attention. Efforts have been made to determine the permeability of the placenta to a number of biologically and clinically important substances. Snyder (69) has reported on the placental transmission of hormones, metabolites, narcotics, and chemotherapeutic agents. Pituitrin, epinephrine, insulin, parathyroid extract, anterior pituitary extract and pregnancy urine extract were injected into the fetuses of guinea pigs, rabbits,

or dogs without evidence of escape from fetus to mother. Byrn & Eastman (70) found substantial amounts of vitamin A and traces of carotene in human fetal plasma. The fetal values could not be raised by increase in the levels of maternal vitamin A or carotene and the authors conclude that the mechanism of placental transfer of vitamin A is still unclear. Lund & Kimble (71) also reported that vitamin A in human fetal plasma is independent of maternal plasma vitamin A but they found that carotene in fetal plasma varies regularly with the carotene of the maternal plasma. They concluded that vitamin A in contrast to carotene either is not transmitted or is poorly transmitted from mother to fetus. Still another view has been expressed by Neuweiler (72) whose evidence led him to believe that both carotene and vitamin A pass through the human placenta but only to a limited degree. Braun & Carle (73) found that the vitamin A content of the bovine fetal liver, although low, is in direct relationship to the mother's diet. This observation suggests that the conflicting results on the relationship between vitamin A in fetal and maternal plasma may be due to variations in the rate at which vitamin A disappears from the fetal blood to be stored in the fetal liver. Experiments with vitamin C and thiamine (74 to 77) indicate that the human placenta is permeable to both. The concentration of lipids in the maternal and fetal blood plasma of sheep has been measured by Barcroft & Popjak (78). Because the lipids in fetal plasma follow approximately those of maternal plasma but at a considerably lower level, it is suggested that lipids pass the placenta to disappear at a considerable rate in the fetal plasma because of storage or other reasons. Ratner (79) has presented the evidence for the passage of native proteins through the placenta. Active immunization of the pregnant mother to diphtheria was reported by Liebling & Schmitz (80) to result in an increased placental transfer of passive immune bodies to the infant. Hutter & Parks (81) have shown that adequate penicillin injected into the pregnant patient at term will result in a bacteriostatic level in the fetal circulation. Greene & Hobby (82) administered penicillin to normal patients in active labor and in most instances found significant amounts in the umbilical cord blood one to two hours later. The placenta of the rat has been found permeable to thiourea (83) and alloxan (84).

Investigations, previously reviewed (85, 86), on the com-

parative physiology of placental transfer using radioactive sodium as the tracer material have been discussed by Gellhorn (87). The results with radioactive sodium substantiate Snyder's conclusion (69) that the rabbit placenta is more permeable at the beginning of the last trimester of pregnancy than at the end of gestation.

Leonard (88) has investigated in the rat the relation of the placenta to the growth of the mammary gland. His results indicate that this placenta is an endocrine organ, an active principle of which works synergistically with hormones of the hypophysis and ovaries to control mammary growth during the second half of pregnancy. In the course of a study on hormones of the human placenta, Finkelstein (89) extracted a substance with the properties of thromboplastin.

*Metabolism and enzymes.*—The problem of the relation between cytoplasmic structure and the fate of different parts of the fertilized ovum during development have been discussed by Runnstrom & Monne (90). Barth (91) has written on the general problems of colloid chemistry in embryonic development. Observations on the respiratory rate and the activity of certain respiratory enzymes in intact embryos and cell-free breis of *Rana pipiens* have been discussed in terms of spatial orientation of enzymes and substrates during embryogenesis by Stiebelman & Steinbach (92).

In chick embryos, Leibson & Leibson (93) have found that blood sugar rises gradually during development, the increase being particularly significant after the eighteenth day when the level exceeds that found in the mature bird. Moog & Steinbach (94) have analyzed chick embryos for adenyl pyrophosphatase activity and found it low up to the sixth day of incubation when it begins to rise. Kugler (95) states that the amniotic fluid of the chick is free of acid-soluble phosphate until the eleventh day of incubation and the small amounts which then appear are largely phosphocreatine and hexosephosphate. In the allantoic fluid, the phosphate is almost completely inorganic; this rises sharply in concentration on the eleventh day possibly, it is suggested, because of the onset of insulin secretion. Lynn & von Brand (96) in a study of the oxygen consumption and metabolism of turtle embryos found that oxygen consumption is about doubled every ten days during the first fifty days of development and obtained

additional data which suggested that large amounts of protein are catabolized during development. The distribution of phosphorus compounds between the skeleton and soft tissues of the chick embryo has been determined (97) and Roche & Mourgue (98) have studied in embryos of sheep and horse the role of phosphatase in the first stages of ossification of embryonic bone. In view of the marked excess of phosphorus over that necessary to fix all the calcium as  $\text{Ca}_3(\text{PO}_4)_2$ , Roche & Mourgue believe that the first stage of ossification consists of independent fixation of calcium and then liberation by phosphatase of phosphoric radicles which unite with the calcium to form  $\text{Ca}_3(\text{PO}_4)_2$ .

The activities of a variety of enzymes have been determined in vertebrate embryos (99, 100). Greenstein & Thompson (101) have found in the rat that some enzymes (arginase, catalase, xanthine dehydrogenase, urea-synthetic systems, and cystine, cytochrome and *D*-amino acid oxidases) are lower in fetal than in adult liver; some enzymes (acid and alkaline phosphatases) are higher in fetal than in adult liver; while others (ribonucleodepolymerase, thymonucleodepolymerase, and amylase) have the same activities in fetal and adult liver. Potter, Schneider & Liebl (102) have analyzed the brain and liver of fetal and newborn rats and compared the activities of succinic dehydrogenase, cytochrome oxidase, and adenosinetriphosphatase with that of the same adult organs. In brain, the enzymes remain constant at a relatively low level from about three days before birth until about six days after birth and then increase sharply to reach the adult level about the thirtieth day. In liver, the enzymes increase rapidly during late embryonic and early postnatal life and approximate the adult level within ten to fifteen days. The authors suggest that their study shows that during the period of increased differentiation and increasing functional load the potential rate of energy mobilization is increased since the activities of both the energy-yielding type of enzymes (respiratory enzymes) and the energy-depleting type (adenosinetriphosphatase) have been shown to rise markedly. The activity of succinic dehydrogenase has also been followed in the developing cerebral cortex of the fetal pig (103). The dehydrogenase activity begins to increase about three quarters of the way through gestation and, unlike that in the rat, is indistinguishable from that of the adult at birth. The activity of succinoxidase has



also been measured and, as with succinic dehydrogenase, changes in its activity have been correlated with cytological changes in the cells of the cerebral cortex.

Other important tissue constituents have been investigated with a view toward understanding changes which may occur as the young animal matures or ages. Ribonucleic acids have been compared in embryonic and adult sheep tissues by Davidson & Waymouth (104). The rapidly growing embryonic tissues appear to be characterized by a high concentration of desoxyribonucleic acid in the nucleus and of ribonucleic acid in the cytoplasm. Conversely, acid-soluble purine nucleotides are present in lower concentration in embryonic tissues than in the corresponding adult tissues. Horvath (105) has analyzed the gastrocnemius muscle of rats aged from 1 to 780 days for compounds (solids, creatine, total phosphate, acid-soluble and acid-insoluble phosphates, hexosephosphates, phosphocreatine, adenosinetriphosphate, glycogen, orthophosphate, and lactate) concerned in muscular contraction. Some of these substances show substantial increases during the initial stages of the aging process, reaching constant levels between 60 and 120 days of age. It is concluded that the diminution in muscular strength in the aged animal cannot be due to lack of these compounds which are important in the chemical processes of muscular contraction.

Macklin (106) has investigated the view that large quantities of iron are stored in fetal liver in preparation for postnatal lack of iron in maternal milk by using the Prussian Blue technique on sections of liver taken from human fetuses ranging from eleven weeks to term. Iron was not found in 60 per cent of the livers which were examined. Hevesy (107) administered radioactive phosphorus to a pregnant mouse and by following radioactivity in the offspring of successive generations concluded that a mouse of the eleventh generation does not contain a single phosphorus atom derived from the first generation.

*Developmental anomalies.*—In the chapter "Prenatal Fate and Foreordination" of *Ourselves Unborn*, Corner (3) discusses the old and current concepts of teratology and the experimental findings which have led to the view that fetal abnormalities may be due to defects of fertilization, to defects of the maternal environment (faulty transportation of the ovum, failure of the maternal



hormone system, mechanical disorder of the uterus, infection of the reproductive tract, infectious disease of the embryo, toxicity, and nutritional defect of the uterine environment) and to defects of the egg, the sperm, and the embryo (genetic defects, and non-genetic constitutional defects).

Investigations previously reviewed (108), have been continued on congenital malformations induced by maternal nutritional deficiency. Warkany & Schraffenberger (109) have shown that the congenital malformations (shortening of tibia, mandible, fibula, radius, and ulna; fusion of ribs, fingers, and toes; and cleft palate) found in the offspring of female rats fed their deficient diet I are prevented when this diet is supplemented by riboflavin. They consequently conclude that absence of riboflavin is responsible for the congenital malformations obtained with diet I. These congenital malformations were obtained in the Sprague-Dawley and Baltimore strains but Wistar rats similarly maintained failed to produce anomalous young (110). Because of these observations, it was suggested that a strain difference exists in the sensitivity of rats to the deficient diet. Noback & Kupperman (111) have now shown that with an appropriate diet much the same external and osseous malformations can be induced in the offspring of female Wistar rats as have been described for the other strains. Congenital defects of the eyes in the offspring of female rats with vitamin-A deficiency have been described by Warkany & Schraffenberger (112). In the abnormal eyes, the lids are fused with the cornea, the anterior chamber is present in a rudimentary form only, the vitreous is missing, having been replaced with connective tissue, and the retina is folded and disorganized. Chondrodystrophy and syndactyly have been found by Cravens, McGibbon & Sebesta (113) among embryos from hens bred with a diet deficient in biotin. Of interest in the light of these animal experiments, is the study by Burke *et al.* (114) on the influence of nutrition during pregnancy upon the condition of the human infant at birth. Of the 216 cases considered, all stillborn infants, all infants who died within a few days of birth, except one, most infants with marked congenital defects, all premature, and all functionally immature infants were born to mothers whose diets during pregnancy were inadequate.

Rumplessness in chicken embryos has been produced experi-

mentally by Landauer (115) and by Zwilling (116); the first by injection of insulin and other chemicals into the yolks of eggs prior to incubation, the latter by transecting the body of the embryo during the second day of incubation. Microphthalmia of chick embryos has been analyzed in regard to its morphogenesis and probable causation by Gruenwald (117, 118). George (119) has described and discussed a pig embryo with bifid notochord, biaxiate brain, and paired hypophyses.

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## PHYSIOLOGY OF HEAT AND COLD

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Within the preceding year or two there have appeared a number of articles which begin to reveal the urgent nature of the problems of temperature regulation encountered by the armed forces of the Allies, and also, something of the measures taken to answer those problems. One of the more notable of these papers consists of the Croonian lectures delivered by Critchley (1) on the general subject of naval warfare under climatic extremes. The idea that the fighting efficiency of the rating is to be preserved and improved, if possible, the need for adequate methods of measuring efficiency, and the fact that practical considerations often limit the kind and the amount of relief that can be provided are all prominent in the lectures. The air conditioning of an entire ship is a problem not to be undertaken lightly because of the weight and size of the necessary equipment. To be considered also is the question of whether the efficiency of the crew will be increased to a degree that will justify the sacrifices made. The matter of insulation is similarly important, and even the proper color of paint is of some significance in determining the crew's comfort. Clothing cannot be designed for thermal protection alone, and a brief insight into the requirements of clothing design emphasizes the need of further experimental study. Critchley concludes with a brief discussion of the selection of personnel for assignments to duty under conditions of climatic stress, and with an interesting speculation regarding the ability of the white man ever to conquer the tropics. His remarks recall to mind the review by Adolph (2) where the testing of individuals for work in desert conditions is approached as a matter of physical fitness. Previous observations suggest that some of the hazards can be obviated by protective devices, that some are overcome through proper acclimatization, while others can be eliminated only by selecting individuals who have either inherited or acquired unusually effective mechanisms of temperature regulation.

## HEAT STRESS

The medical experience of American forces stationed in the Middle East has been summarized by Sams (3), with brief mention of the effects of the extreme heat and humidity encountered in certain areas. The well known blood dilution and apparent anemia of chronic heat exposure were noted, together with a more or less permanent dilatation of vessels of the skin and a generalized lowering of systolic pressure, the latter phenomenon being especially noticeable in men whose pressure was previously within the hypertensive range. The most remarkable changes in the psychological reactions of the men were their shortness of memory, absentmindedness and forgetfulness, irritability, and difficulty in concentrating (4). British experience in the heat of Iraq has been described in somewhat greater detail by Morton (5), with records which vivify the exceptionally high temperatures (up to 125° F.) encountered during the five months of the hot season. The main emphasis of the report is upon the diagnosis and treatment of conditions resulting from overheating (see below); many other problems are touched upon, however, in the discussion which follows the paper, where members of his audience contributed freely and informally of their own experience in hot climates. The meaning of the word "acclimatization" was considered without arriving at a satisfactory definition, and the matter of appropriate tropical clothing was likewise discussed without definite conclusions. American insistence upon air conditioning of operating theaters, hospitals, and barracks was regarded as an important contribution to the welfare of troops. Ladell, Waterlow & Hudson (6) have also described their experience in caring for men under conditions of tropical heat. They found it remarkable that their normal subjects appeared to be in a state of chronic dehydration, as judged by weight loss, low twenty-four-hour urine volume, and elevated blood urea, in spite of the fact that their water intake apparently equalled their water loss. The dehydration was therefore attributed to a slightly insufficient intake of salt. In these experiments the salt content of the sweat was found to increase toward the end of the hot season; this was interpreted as an early evidence of incipient failure of heat regulating mechanisms. The interpretation is consistent with the finding that two general types of heat exhaustion occurred in this climate—one, early in the summer, was evidently characterized by a salt deficiency dehydration and was so treated successfully;



the other appeared late in the season, was characterized by polyuria and diminished sweating, and was thought to be a result of generalized failure of defense mechanisms.

Not all heat exposure occurred in the desert or in the tropics. Chambers (7) found men working in the ship's engine room and stokeholds at dry bulb temperatures of 110 to 132° F., with a relative humidity of 78 to 87 per cent. The men were presumably fairly active, yet they appeared to suffer no ill effects from the heat because they were evidently well acclimatized to their environments. The importance of protection against stresses imposed by light, heat, and humidity is well recognized in the field of industrial medicine (8, 9). In a survey of working conditions in a selected group of Massachusetts industries, excessive "effective" temperatures were found in most of the workrooms where wet processes were carried on. Poor design and misuse of ventilation systems were common, even though methods are available for adequate protection of workmen under these conditions (10).

Progressively more emphasis is being placed upon acclimatization as a temperature regulating mechanism in man (11), with the desirable result that man's reactions to temperature changes are proving to be more nearly like those of the usual experimental animals. In man the reactions take longer to develop. The time required for metabolic adaptation to heat has been emphasized by Mills (12, 13); according to his observations two to three weeks are consumed in effecting this type of adjustment in experimental animals. When acclimatization to heat has been achieved, the animals require relatively more choline and thiamine in their diet. Further study of these metabolic problems is highly to be desired, for although the effects of acclimatization upon the vascular system, the blood, body water, and electrolyte distribution are fairly well known, the adaptations evoked in the intermediary metabolism by prolonged temperature stress are still largely undiscovered.

Quantitative data on the upper limits of environmental temperature under which men can work have become more reliable. Taylor (14) has devised a formula from which one may predict whether or not a given set of conditions is tolerable for thirty to sixty minute periods, and he has experimentally verified the predictions made from this formula by means of observations upon unacclimatized subjects working at relative humidities of 10, 50, and 90 per cent. The men were able to tolerate a 60 minute ex-

posure to 63° C. (145.4° F) when humidity was 10 per cent, but at 90 per cent humidity, 40° C. (104° F.) was the upper limit of heat tolerance (evidently the dry bulb reading). Eichna and co-workers conducted a laboratory study of human heat tolerance using as subjects "acclimatized" men, and they, too, found humidity to be an important factor (15, 16). Sustained (four hours) marching at a rate of three miles per hour without clothing, under a twenty pound pack, was easy at a wet bulb temperature of 91° F., difficult at 91 to 94° F., and all but impossible above 94° F. The results of the experiment agree with those of Haldane that the wet bulb reading is a reliable index of man's ability to work. Sweating at a rate of 3.5 l. per hour was noted. Robinson, Turrell & Gerking made similar observations under even more variable experimental conditions where the rate of energy expenditure was directly measured and correlated with the subject's heart rate, rectal and skin temperature, and rate of sweating (17). Data so obtained were used for the formulation of an "index of physiological effect" which expressed the men's reactions. The conclusions drawn from all of these studies are not new, inasmuch as the effect of humidity, clothing, and work upon heat tolerance are well known; what is new is the presentation of these carefully measured data which go far to remedy the existing lack of quantitative information (18, 19). These data also emphasize the need for an adequate method for expressing the physiological equivalent of temperature, whether by means of some arbitrarily chosen "effective" temperature or by some other scheme (20). The work of Eichna and his associates indicates that wet bulb readings must have a dominant place in any such expression.

A method by which the effect of humidity may be studied under controlled conditions has been devised by Kligler, Guggenheim & Schwartz, who kept rats in cages suspended in a constant temperature bath (21). Through the cages was drawn a current either of dry air or of air saturated with water. They found that rats acclimatized to the humid atmosphere drank 19 per cent more water and excreted slightly less urine, urinary chloride, and urinary nitrogen upon being placed in a dry atmosphere. Conversely rats acclimatized in dry air excreted more urine and more chloride and nitrogen upon being placed in a moist environment. Thyroidectomized animals did not show this effect upon being moved from dry to humid conditions. The reactions appear to be a part of the acclimatization processes, and doubtless have to do with the

fact that dry and saturated atmospheres present quite different problems of temperature regulation.

*Overheating.*—Heat exhaustion and sun "stroke" have been common enough to have provoked several interesting descriptions of their symptomatology and treatment, as well as a considerable amount of experimental study, the results of which are not yet available. [Note the censoring of the papers given at a symposium on fatigue (22).] Wallace, who reviewed cases of heat exhaustion encountered during training in Mississippi, emphasized the fact that hot weather clothing should not hinder the evaporation of sweat, and that acclimatization processes (of unspecified nature) confer a significant element of heat resistance (23). The paper contains a list of suggestions suitable for the instruction of nonmedical personnel in the basic principles of avoiding overheating. Croom's brief description of seventy-one cases of pyrexia among men disembarked from a single large transport illustrates how disregard of such principles may have serious results (24). The men were not acclimatized to heat, they were already dehydrated because of restricted water intake during the last few days of the voyage, and upon disembarkation they were marched four miles in the heat of the day, without opportunity for drinking. Among the severe cases of heat stroke the rectal temperature exceeded 108° F. Fever was controlled by cold water sprayed upon the skin and administered as rectal enemata; fluids were not given parenterally because, when the temperature had been controlled, they could be taken by mouth. Shepherd's experience was quite similar in this regard, since he, too, found that men who had to march soon after disembarkation were particularly vulnerable to heat (4). Cases of all degrees of severity were encountered, and an attempt at classification into four categories was made, viz., acute heat stroke, subacute effects of heat, heat pyrexia, and heat exhaustion [see also (11)]. Prompt treatment was found to be imperative. A somewhat different classification was adopted by Borden, Waddill & Grier under the headings of heat cramps, heat prostration, heat exhaustion, and heat stroke (25). The authors emphasized the importance of sacrificing the military training schedules of troops upon occasion in order to avoid subjecting them to the hazards of overheating. Under combat conditions, such a procedure would be impossible and protection would have to be sought by other means. The series of cases presented by Moore (26) illustrates some of the precautions which may spell survival to airmen forced down in the

jungle or the desert. All of these papers, and the many others which preceded them, emphasize once again that man is utterly dependent for life upon his ability to hold his body temperature within a narrow range, and that other goals sometimes must be abandoned to this end.

*Solar heat load.*—In military practice as well as in industry, risk of overheating occurs under two general types of environmental conditions, namely, (a) when a machine or engine is the principal source of heat, and (b) when the sun is the principal source. Superstition has persisted to the effect that the sun's rays have some unfavorable effect upon man apart from their heat producing ability, and that sun stroke is to be attributed to this unknown influence. War experience, however, has hastened the discarding of superstition at the same time that it has stimulated research upon the quantitative aspects of solar radiation as applied to the problems of physiological temperature regulation (27). Molnar, Towbin & Brown (28) measured the effect of solar radiation upon thermal equilibrium in man, and found that positive heat gain occurred only under conditions where the sweat loss equalled or exceeded 125 to 150 gm. per hr. The rate of gain increased about 30 kcal. per hour per man for each rise in solar intensity of 60 kcal. per sq. m. normal incidence per hr. Maximal gain was 200 kcal. per hr. Gosselin, who performed a similar experiment but who studied also the effect of environmental temperature, noted that his subjects gained 200 kcal. per hr. at a dry bulb temperature of 100° F., and that there was an increase of about 11 kcal. per hr. for each degree (Fahrenheit) of rise of air temperature (29). At night at an air temperature of 100° F. the heat gain was 100 kcal. per hr. less than at the same temperature during the afternoon. Gosselin found that clothing diminished total heat gain by 100 to 140 kcal. per hour at 100° F. At somewhat lower temperatures (75 to 91° F., dry bulb), Molnar, Towbin & Brown obtained a somewhat smaller effect from clothing, a diminution of 40 to 80 kcal. per hour (28). In both series of experiments heat gain was estimated by subtracting evaporative heat loss from heat production (calculated from oxygen consumption), with a small correction for heat storage.

That the quantitative estimation of heat exchange is not a simple procedure has been emphasized by Blum (30). Ideally the heat gain from metabolic oxidations, the total solar heat load (direct from the atmosphere and reflected from the earth), and gain

by long wave radiation from the terrain must be weighed against heat lost by long wave radiation to the "heavens," by evaporation, convection, and conduction. Blum set up an hypothetical balance sheet which lists the magnitude of each factor under a given set of arbitrarily chosen conditions. For any other set of conditions different figures must be used. According to Blum, the number of variable factors to be considered is large enough and their effect of sufficient importance as to cast doubt upon measurements in which all of them have not been accounted for in some manner. To take such an account is obviously not easy, and the author suggests more general use by physiologists of data now used only by physiologists, meteorologists, and astronomers. Considering the fact that in the experiments of Molnar *et al.* and those of Gosselin each of these factors was not specifically taken into account, the agreement between their results and the calculations of Blum is worthy of mention, because it suggests that by suitably controlling the conditions of the experiment, certain of the factors mentioned by Blum may be disregarded. In this field there still appears to be room for profitable study of a quantitative nature. Blum & Terus (31) have attempted such an investigation of the sunburn preventive qualities of ointments. Thus far only the observation that the protective qualities of the preparations tested varied with the subjects' susceptibility to sunburn has been made public. Blum has also reviewed the whole field of study of the physiological effects of sunlight on man—a topic which covers much more than temperature (32).

#### THERAPEUTIC USE OF HEAT

Ober (33), under the auspices of the American Medical Association's Council on Physical Medicine, has summarized the use of heat in the treatment of surgical and orthopedic conditions; briefly, heat is useful whenever it relieves pain, swelling, or spasm, or through its influence on the circulation facilitates defensive or repair processes. In the presence of traumatic shock, the "prolonged" use of heat appears to be contraindicated because it produces a rise in heart rate and venous pressure, a fall in arterial pressure, dehydration, and symptoms of nausea, vomiting, headache, muscular pains, and exhaustion (34). The experiments in question, however, were performed upon normal subjects—that is, the effect of heat upon shock was not studied directly. Patients with angina pectoris experience relief of their symptoms in warm environments where they are able to do work which under cooler conditions

evokes an attack of pain (35). Local application of cold to the patient's hand tends to provoke an attack during exercise, and this has been proposed as a valuable diagnostic test. Temperature changes are thought to act reflexly upon coronary vessels (36). The significance of fever as a therapeutic aid in influenza has been discussed, although the data reported yield only circumstantial evidence that the febrile response *per se* shortens the disease (37). Used therapeutically, fever has certain hazards, since it frequently produces cyanosis, bilirubinemia, and circulatory collapse (38). The administration of oxygen and carbon dioxide appears to lessen the incidence of collapse although no effect upon the anoxia was noted. In the opinion of the authors, hyperthermia should be regarded as a procedure comparable to a surgical operation, and should include adequate preparation and after care.

#### COLD STRESS

Responses of the body to cold, with emphasis upon aviation physiology, have been reviewed by Kossman (39), while the experience of aviators forced down in Arctic waters has been described by Kelsey (40). An editorial published in *Lancet* indicates that both German and Russian scientists are also interested in the problem of cold stress (41). It will be interesting to learn the details of the procedures and apparatus with which the Armed forces of the various nations sought to protect their men against temperature extremes. What little information is now available indicates only the gravity of the problem and that, by the Allies, at least, it was ultimately well handled in the Air forces if not in troops assigned to other services (42). Under some conditions protection was difficult if not impossible, as in the Attu campaign in 1943 where the men were exposed to zero and subzero weather for fourteen days. Necrosis that progressed to gangrene requiring amputation of the toes or feet occurred, especially in battalions where regular, systematic attention was not given to the care of the feet (43).

Medical means of preventing tissue loss from frostbite have been under investigation with exceedingly encouraging results (44, 45). The experiments made use of the fluorescein injection technique for studying the state of the cutaneous circulation in rabbits subjected to freezing of selected areas of the skin. Under ultraviolet light the condition of the cutaneous vessels could be observed rather easily. For a period of 30 to 120 minutes following



the application of cold, the circulation through the area could not be demonstrated; this period was followed by an interval of some hours in which the dye content of the area was greater than normal, suggesting dilatation of the vessels; at the end of this period the vessels became closed again, and biopsy revealed clumping of cells in the arterioles and capillaries. Later, true thrombosis appeared, and gangrene began. Believing that the gangrene was the result of the clumping and thrombosis, the authors gave a group of rabbits heparin after the refrigeration. Where the sixteen control animals all developed gangrene, only two of the heparinized rabbits showed any surface lesions at all, and no gangrene occurred. From this exciting discovery the experiments were transferred to volunteer human subjects in whom similar results were obtained. Ultimately an opportunity came for treating with heparin a patient suffering from prolonged cold exposure; he recovered without permanent loss of tissue. The experiments are not yet extensive enough for general clinical adoption, but they appear to hold great promise of future usefulness (46).

*"Immersion foot."*—The lesion known as "immersion foot" is one of the frequent results of exposure to wet cold, even though it may occur in subjects exposed to water of rather mild temperature. In the opinion of those who have studied this intensively, "immersion foot" is not synonymous with frostbite because in the former actual freezing of the tissue does not occur (47, 48). Prolonged chilling is the important etiological factor, and it appears selectively to affect nerves and blood vessels of the exposed extremities (49). The pain associated with the necrosis has been attributed to anoxia in the early stages and to contraction of scar tissue around the nerves in later periods (50). Treatment is directed toward reducing the metabolic requirements of the tissue by local cooling until the circulation can be gradually restored through the injured area. Early pain is relieved by cold (50), while that which occurs a few days later is relieved by heat (47). (The responses of the circulation to cold are also considered below.) Sir Thomas Lewis extended his observations upon the phenomenon of supercooling of the skin, that is the induction of subfreezing temperatures without freezing of tissue, and noted that by appropriate technique whealing can be evoked in almost every subject. The whealing is similar to that which occurs in the presence of true frostbite, and it is evident, therefore, that in treating cases of suspected frostbite one must attempt to eliminate those in which only

supercooling has taken place, since treatment of the latter condition is unnecessary (51).

#### THERAPEUTIC USE OF COLD

*Refrigeration anesthesia.*—Local application of cold is proving a useful therapeutic procedure in a variety of conditions (see previous volumes of the *Annual Review of Physiology*). Its widest use is in the preparation of extremities for amputation, especially in patients who are judged to be poor risks for general anesthesia and major surgery. Most of the reports are enthusiastic, since the authors believe that in this way the mortality rate is lowered and operations that would otherwise be difficult or almost impossible become relatively easy (52 to 60). The use of refrigeration in place of other types of anesthesia has not gone unchallenged, however, although present criticism concerns more the place of refrigeration in the field of surgery and its possible effect upon wound healing, rather than its usefulness about which there seems to be general agreement (61, 62, 63). That retardation of healing occurs is admitted even by proponents of the method (53, 60), and for this reason and because a certain amount of injury to nerves within cooled tissue has been noted, a few surgeons have elected to use refrigeration for its beneficial effect upon the traumatized or avascular extremity in preparation for amputation, rather than for its anesthetic effects (64). Allen (65, 66) has made a spirited reply to those who have questioned the efficacy of cold anesthesia, and his protest has been seconded by Kross (67), while "good" or "excellent" anesthesia has been reported in "most" patients of a series of some thirty amputation cases at New York City hospital (68). Measurement of tissue temperature indicates that to achieve favorable results it is necessary to apply refrigeration for not less than three hours with a tourniquet in place for a minimum of two hours, thereby producing a skin temperature of 40 to 50° F. in the region of the operation and of 45 to 65° F. one and one-half inches below the skin surface. In cases where an attempt is to be made to save the limb by prolonged cold application, a skin temperature of 70° F. is recommended. Damage which occurs following such treatment may be the result, not of the cooling, but of rapid warming at the end of the cold period; this rapid warming causes tissue changes closely resembling a burn.

At the time of this writing a final appraisal of the method can-



not be given. It appears evident from the number of favorable reports that the therapeutic use of cold is a significant contribution to surgical practice, whether or not all the claims of its proponents are completely substantiated. Further study may yield even more impressive results, especially if the claim of Kross (67), that by this procedure the necessity of amputation may be avoided, proves to be generally useful. The basic tenets of Allen's method appear to be well grounded, in that cooling tissue obviously lowers the rate of energy exchange (69). It remains to be determined under precisely what conditions and to what extent this is a desirable achievement.

Cold application (6° C.) has been successfully used in place of morphine for the relief of pain following surgical operations, including laparotomies and amputation of the breast. No ill effects were noted (70). Similarly favorable results were obtained in dental practice from cold anesthesia of the maxilla or mandible. The method of production of this anesthesia appears to be relatively simple and the apparatus required is not prohibitively complex (71). Cold has long been successfully used in dermatology (72), and it has now been employed in the treatment of malignant tumors of the skin with what appears to be remarkable success (73). Publication of the end results of this treatment will be awaited with great interest, since the method is said to cause only inconspicuous scarring, less than would have followed irradiation or surgical removal of the tumor. Similarly provocative is the suggestion that local cooling constitutes an effective method of treating burns (66, 74).

*Recovery from shock.*—At least two more attempts have been made to measure the effect of hypothermia and hyperthermia upon survival following hemorrhage. In the former report (75), dogs which had been bled enough to make their ability to survive questionable, were then placed at one of four environmental temperatures. At 52° F., 38 per cent died; at 72° F., only 18 per cent; at 85° F., 45 per cent died; and at 95° F., 93 per cent failed to survive. The author concluded that either heat or cold is a definite liability following hemorrhage. The second paper (76), also concerned with the survival of dogs subjected to hemorrhage, reported that animals with a rectal temperature below 35° C. survived longer than those with temperatures above that level. Ultimately all of the dogs died (with the exception of one "hypothermic" animal). In hemorrhage of this severity, therefore, the practical value of hypo-

thermia is "debatable." The results of each of these experiments agree with previously published work.

A major difficulty in the study of shock has been the production of reproducible shock in order to be able to assess the effectiveness of therapy. To this end, standardized methods of bleeding and of traumatizing experimental animals have been devised in various laboratories. It is now evident that any attempt at standardization is in vain unless the environmental temperature is regulated within narrow limits (75, 77). At 16° C., 83 per cent of the animals survived a standard trauma; at 20° C., 86 per cent survived; at 24° C., only 38 per cent, and at 28° C., only 10 per cent lived. Moreover, dogs kept in a warm environment could be saved by local application of cold (ice bags) to the traumatized extremity [cf. (67)]. The authors discovered that much of their previous difficulty in attempting to obtain standard degrees of shock was hereby explained, inasmuch as when temperature was not controlled, dogs died in the summer experiments while, during the winter, recovery was the rule. A similar temperature effect has also been noted in tourniquet shock in the rabbit, but the results obtained in this experiment were not as uniform as in the previous study upon dogs (78).

The protection conferred by cold against anaphylactic shock in the rabbit has been found to depend somewhat upon the size of the dose of antigen used to evoke the shock. With smaller doses the degree of protection is more noticeable than with larger doses (79). This observation was explained on the grounds that the sensitivity of the rabbit to epinephrine is decreased in hypothermia (80).

#### MECHANISMS OF TEMPERATURE REGULATION

*Skin.*—Of first importance among the body's mechanisms of temperature regulation is the skin, since the regulation of surface temperature determines to a large extent the rate of heat loss from the body as a whole. A comprehensive review of this subject is given in that encyclopedic volume, *Medical Physics* (81). No little difficulty has been encountered in providing suitable clothing for troops, not only because the requirements of men under combat conditions vary so widely, but also because data were not available for satisfactory use of fabrics and for clothing design (see above). Improvements have been made, but much remains to be achieved in the field which has been called "textile engineering" (82). The effect of clothing upon a man's ability to work in the heat is equally

as important as protection against cold. No matter how light it is, clothing definitely hinders temperature regulation in hot environments because it limits the vaporization of water. As a result of this limitation, the clothed subject cannot tolerate work at as high a temperature as the nude subject. Shelley *et al.* (83) found that a coverall of herringbone twill reduced by two degrees the temperature at which a standard work load can be performed.

A brief report on the effect of temperature upon the electric potential of the skin of the fingertips suggests that positive potentials are increased by warming the skin (84).

*Circulation.*—Many investigators have measured blood flow through the arm by means of the plethysmograph, and have noted that the rate of flow depends upon the temperature of water in which the limb is immersed. Their results have been brought together and compared with the results of an independent study of the problem by Barcroft & Edholm (85). Temperatures of 20 to 32° C. cause an almost immediate decrease in rate of flow, which then remains relatively constant for several hours. A temperature of 35° C. evokes almost no change. At higher levels (38° to 42.5° C.) a prompt rise occurs, followed by a fall to a level which is then maintained for at least 3 hours. At 45° C. a continuous rise was observed. To stabilize the rate of flow at a temperature between 35 and 42.5° C., the arm must be immersed at a constant temperature for a period of approximately two hours. Measurements of the temperature within the depths of the antibrachial muscles showed that upon exposure to cold water the deep temperature was always above that of the water, while in warm water the arm was invariably cooler than the water. Circulatory adjustments in the vessels supplying the muscles were therefore said to account for the major part of the alterations in rate of total flow observed in these experiments.

Using an indirect method of calculation of blood flow based upon the rate of heat loss from the hand, Speakman (86) has calculated the relative rates of blood flow when the hand was immersed in water at 5, at 10, 15, 20, or 25° C. In confirmation of the results of Barcroft & Edholm (85), the rate of flow was less at 15° than at 25° C., but at 10° and at 5° a definite increase in flow was observed. Direct measurements with the plethysmograph verified in a "qualitative" way the results obtained by the indirect method. Further confirmation was later obtained from a more extensive series of determinations using the venous occlusion (plethysmographic)

method, by means of which the increased flow at lower temperatures ( $5^{\circ}$  and  $10^{\circ}$  C.) was easily observed (87). A technique closely related to the indirect method employed by Spealman was used by Moses & Ferderber (88) to study the blood flow in the arms of normal subjects and patients with vascular disease. They found the rate of flow in the latter group to be decreased by about one-third. In their experience oscillometric readings and measurements of skin temperature were less reliable indicators of the state of the vascular bed.

The reaction of blood vessels to cold is an important factor in the etiology of the immersion foot syndrome (89, 90), as well as of other types of vascular disorders seen frequently in military experience (49). Cold rather than emotion was found to be the excitant mechanism in one hundred unselected male patients with Raynaud's disease examined at the Mayo Clinic (91). Though in the Mayo series this disease occurred four times more frequently in women than in men, the number of male patients was fairly large (198 in twenty-two years). Whether or not cold exposure of the body as a whole or local cooling of the skin affects the blood vessels of the nasal mucosa is a debated question, but recent evidence indicates that there is such an effect (92). Under appropriate conditions reflex swelling of the mucosa with or without an elevation of temperature, and an elevation of the temperature of the mucosa with or without swelling were observed. The relation of these changes to the onset of acute upper respiratory infection is unknown.

Evidence that generalized severe hypothermia has a selective unfavorable effect upon the circulatory system of the rat has been obtained by recording the heart rate, blood pressure, and electrocardiogram (93). The usual course of fatal hypothermia appears to be as follows: first (rectal temperature falling from  $38^{\circ}$  to  $28^{\circ}$  C.), a period of compensatory circulatory adjustments, characterized by peripheral vasoconstriction and bradycardia with increased stroke volume; second ( $29$  to  $20^{\circ}$  C.), progressive circulatory failure accompanied by further slowing of the heart, arterial hypotension, and reduced cardiac output as a result of decreased stroke volume; third (below  $19^{\circ}$  C.), a phase of "regional asphyxia" marked by impaired ventricular contraction, atrioventricular block, and signs of impending failure of central nervous system respiratory mechanisms. The sinoatrial node appears to be especially sensitive to cold, since abnormalities of the P wave invariably

appear when the rectal temperature has reached 17° C. Even with smaller changes of body temperature (no more than plus or minus 5° C.) in the rat, significant alterations of heart rate and blood pressure occur (94). In hyperthermia, tachycardia and hypertension appear; in hypothermia, bradycardia and hypotension, followed by a return of heart rate and blood pressure to levels approximately normal or just above normal. When blood pressure or heart rate are to be measured in the rat, care must be taken to prevent changes in body temperature.

*Water and electrolyte equilibria.*—The nature of the organism's dependence upon water and ionic equilibrium for resistance to overheating has been further studied (95, 96, 97). Administration of potassium chloride solution (98) has been found to increase the frog's resistance to heat (39 to 40° C.). In man, ability to work in hot dry or hot humid environments depends largely upon his water intake. Pitts, Johnson & Consolazio (99) investigated this relationship in subjects acclimatized to intermittent exposure to heat, marching at a fixed rate up a constant slope. When water was not taken, their body temperature rose steadily (to 102° F.), they tired easily and worked inefficiently. Upon an *ad libitum* water intake their temperature rose but not so much, and they finished the exercise in much better condition. When they were required to drink enough water to replace their loss as sweat, performance improved still further and body temperature rose little or not at all. The obvious conclusion is that water drinking is to be encouraged during work in heat. The effects of salt or glucose administration were less apparent; given without water, both produced gastrointestinal discomfort without improvement in heat tolerance. Given with water they brought improved performance, but it was not clear whether this was to be attributed to the salt (or glucose) or to the water. In subjects receiving adequate amounts of salt with their meals (as these were), extra salt evidently is not indicated. The remarkable improvement obtained by administration either of water or of 0.2 per cent saline in amounts equal to the rate of sweating raises the question whether ability to work would have been better or worse on *ad libitum* saline than on *ad libitum* water. The experiment was not done, or at least, not reported.

Saline has been found to be less palatable than water by men previously dehydrated by work in desert conditions. When they were given cool water, however, dehydrated men rehydrated themselves quite promptly up to the level of hydration of men with free

access to water during the work period. Pilocarpine did not decrease drinking after dehydration in spite of its strong effect in increasing salivary flow (100). Adolph (101) compared the heat resistance of different species with their ability to increase evaporative water loss, and also with whether or not they drink during the heat exposure. There was a considerable variation. The rat, which pants little and drinks little, withstood only 38° C. dry bulb for eight hours, where the dog, which both pants and drinks, withstood 53° C. for at least thirty-two hours. Death from overheating was the result of decreased heat transfer as a result of failure of the peripheral circulation.

Results of a carefully controlled study of water balance, including intake, output (renal and extrarenal), and distribution within the body at different environmental temperatures have been published by Conley & Nickerson (102). Insensible water loss was notably uniform while the subject remained at a constant temperature, but changed abruptly when the temperature was altered. Decreases and increases of plasma volume, previously reported, were readily observed. The kidney excreted sodium and chloride in amounts appropriate to the intake and to the extrarenal loss (in sweat) of each. Otherwise the results were largely negative, possibly because the subjects were not really exposed to the temperature extremes chosen for the experiments, since "in all experiments the subjects were permitted to select clothing suitable to each environmental condition." Here was undoubtedly their most important mechanism of temperature regulation.

*Sweat.*—The rate of sweat excretion by different areas of the body may be measured rather simply by the following technique (103):

The area selected was dried for 10 sec., and then a brass ring 7 cm. in diameter and 2 cm. deep was held lightly pressed down on the area. The ring carried a well fitting lid, to minimize evaporation. . . . The ring prevented sweat trickling away from the area or reaching it from adjacent areas. After 2 min., the lid was removed, and, during the next  $\frac{1}{2}$  min., the sweat within the ring was mopped up by means of a previously dried and weighed cotton pledget. The increase in weight of the pledget was then determined.

In subjects sweating profusely as the result of work in a hot, humid environment, about 50 per cent of the total sweat secretion occurred on the trunk, 25 per cent on the lower extremities, and 25 per cent on the head and upper limbs. That the palms and soles sweat little illustrates the fact that there is a rather considerable differ-

ence between the intensity of sweating of different regions of the body. The data substantiate in quantitative fashion the conclusions of previous investigators.

The restriction placed by clothing upon the evaporation of water from sweat seriously handicaps temperature regulation of a man working in a cold climate unless he is "underdressed" to a point where the low environmental temperature facilitates the dissipation of heat produced in exercise to such an extent that profuse sweating does not occur. When fully clothed, this heat cannot be easily lost, excessive sweating occurs, and the clothing becomes laden with moisture which gradually evaporates during rest periods and robs the body of heat which it can ill afford to lose at that time (104).

Subjects unable to sweat are severely limited in their tolerance to heat. The deficiency may be congenital (105) or acquired (106), although the latter is said to be quite rare. Physicians in military service, however, have seen a fair number of cases of what they have described as "thermogenic anhidrosis," where the ability to sweat is temporarily lost (107 to 110). As observed by Wolkin *et al.* (107), the condition was said not to be the result of salt depletion, but this has been questioned by Miller (111).

*Skeletal muscles.*—The onset of shivering in men exposed to cold was delayed or inhibited when the subject breathed pure oxygen from a closed circuit metabolism machine. This inhibition was accompanied by a subjective sensation of warmth, although the skin temperature changed little or not at all. Total oxygen consumption did not diminish when shivering was inhibited, which suggests that "detectable" shivering is not prerequisite for the increase in metabolic rate during cold exposure (112, 113). From the published notes it is not clear that the effects observed may not have been partially attributable to the extra effort associated with breathing from the metabolism machine.

Browman has been able to show that the normal diurnal cycle of spontaneous activity in the rat is derived in part from variations in the temperature of the environment (114, 115). Normal rats run more in the dark than in the light, regardless of the temperature of the two periods; but if light sensitivity is destroyed by blinding the rats, they then run more in cool than in warm periods of the day. The author suggested that these two tendencies, viz., to run in the dark and in cool environments, account for the rat's being a nocturnal animal, and also influence the time of onset of estrus



in the female. By maintaining the animals alternately in light at 27° C. for six hours, followed by six hours of dark at 16° C., it was possible to induce two peaks of activity within a twenty-four hour period rather than the one peak normally observed.

*Metabolic rate.*—Temperature has a remarkable influence upon the metabolic rate of starved rats (116). Rats fasted at a temperature of 20 to 24° C. survived only nine days, and on the last day but two of the fast had a metabolic rate that was over 50 per cent of the standard normal rate. Starved at 30° C., rats survived almost twice as long (seventeen days) and had a metabolic rate 33 per cent of the standard rate two days before death.

Where previous attempts were unsuccessful, Swift has now shown that feeding does affect the critical temperature of the rat (117). The minimal rate of oxygen consumption occurs at a temperature about 1° lower in the fed than in the fasted state, since the assimilation of food is, in itself, a significant extra heat load for the animal. The range of critical temperature as measured by this method is fairly wide, however, extending over 5° C. (28 to 33° C., fasted).

*Diet.*—Because foods vary in their effects upon metabolism, and because metabolic requirements vary with temperature, the composition of the diet is of vital importance to men forced to live under conditions of temperature stress (118, 119). A method for the preparation of emergency rations for polar flights has been described, including menus capable of furnishing about 2500 Calories in a quantity of food weighing only about 700 gm. (120). Most of the foods were dehydrated and processed into blocks measuring 2×2×0.9 inches; they were to be rehydrated before use. Preparation of food for tropical diets also poses certain problems, one of which is the providing of appetizing food in order to stimulate food intake (121). Another is the composition of the diet, specifically whether the heat of utilization of a food such as protein places an added burden upon mechanisms of temperature regulation (122). Pitts, Consolazio & Johnson (123) found that altering the protein content of the diet had no demonstrable effect upon the work performance of human subjects in a hot, humid environment. They regarded the extra heat production associated with protein utilization as a negligible factor under the conditions of their experiment where the heat exposure was only intermittent. No observations upon the effect of high protein diets upon subjects continuously exposed to heat were included.



An interesting summary of the results of almost nineteen years of feeding experiments in the rat proves beyond question that both the food intake and the rate of weight gain are greater in winter than in summer (124). The number of calories required to yield one gram of gain, however, was least in the spring and summer and greatest in the fall, which suggests that food is used most efficiently in the former and least efficiently in the latter seasons. The variation probably arose from the temperature stress to which the rats were subjected, and well illustrates the importance of performing feeding experiments in constant temperature rooms.

*Vitamin therapy.*—The efficacy of vitamin administration for the improvement of tolerance to extremes of heat and cold is still not established. Maycock found that the intravenous injection of thiamine did not increase the rate of survival of rabbits subjected to hemorrhage and to the application of cold to the intestine (125). Exposure of the rat to high temperature apparently does not alter the tissues' content of the various B vitamins (126), nor does the intake of extra vitamin C or the B vitamins improve the performance of men exposed to high temperatures for two to four days (127). The effect upon longer exposures is not reported.

The mechanism of the depression of food intake in hot environments remains a mystery. In man, at least, this depression apparently is not derived from any decrease in gastric motility, since gastric emptying time is less at 120° F. than at 77° F. (128). However, the higher temperature had no appreciable effect upon appetite in the experiments in question.

*Endocrine glands.*—Continuing the search for the explanation of the cold sensitivity of thyroidectomized animals, Leblond & Gross (129) found that gradual acclimatization to cold confers a significant degree of protection upon thyroidectomized rats, and that heavier rats are more resistant than lighter ones. They noted also that whereas the food intake of thyroidectomized rats was about 86 per cent of the normal intake at "room temperature," at 0 to 2° C. both groups ate the same amount. Cold exposure was better tolerated within a few hours of removal of the thyroid than it was two weeks after the operation. That neither thyroidectomy nor removal of the adrenal medullae prevents the normal increase of metabolism upon cold exposure is suggested by the work of Morin (130), who also found that the extra heat produced in a normal dog given epinephrine was utilized by the animal as a mechanism of temperature regulation during cold exposure (131).

The ability of the adrenal cortex to confer resistance to cold is well established (132, 133). An assay method for adrenal cortical extracts based upon this property has been proposed by Roos (134); the test compares the potency of the extracts in preventing hypothermia in young, adrenalectomized rats exposed to 1° C. So far as heat exposure is concerned, death followed a four hour exposure of adrenalectomized rats to a temperature of 38.7° C., where normal rats and rats treated with desoxycorticosterone or with adrenal extract survived the exposure (135). Since desoxycorticosterone, which acts mainly upon electrolyte and water exchanges, was quite as effective as adrenal extract, the authors concluded that the deficiency exhibited by the adrenalectomized animals was probably concerned with sodium metabolism. Where the adrenals are normal, however, the injection of large doses of adrenal extract does not further improve the tolerance of human subjects nor their ability to work in the heat. Yet both adrenal extract (136) and desoxycorticosterone acetate appear to reduce the sodium chloride content of sweat (137).

Additional examples of the effect of environmental temperature upon the sensitivity of animals to hormonal preparations are to be found in the reports that mild cooling depresses insulin sensitivity (138), while, as judged by the induction of ovulation, rabbits are more sensitive to anterior pituitary hormones in July, August, January, and February than they are during the months of the spring and fall seasons (139).

*Central nervous system.*—Throughout the period of the war, whatever notable contributions may have been made to knowledge of the central nervous control of body temperature have not been made public. The few papers which have appeared recently represent isolated observations, scarcely capable of integration with one another in a review such as this. Greenberg *et al.* (140), for example, found that "postural polypnea" (which occurs at room temperature when a goat or other ruminant is held in the dorsal recumbent position) can be abolished by exposing the animal to a temperature of 0° C. A similar result was achieved by the intravenous injection of a "massive" quantity of physiological saline. Keller (141) has reported that fibers subserving the function of temperature regulation traverse the lateral portions of the upper pons; and further, that fibers concerned with heat production (protection against cold) lie ventral to those controlling heat loss (protection against heat). The origin of the fever associated with inflammation has

been ascribed by Menkin to the release from injured cells of a nitrogenous substance, "pyrexin," which has been recovered from the euglobulin fraction of exudates. Its site of action has not been identified (142), but it is assumed to act upon neurons responsible for temperature equilibrium. The suggestion has been made that aspirin produces its antipyretic effect at least partially through these same neurons, since monkeys with bilateral hypothalamic lesions do not sweat as normal monkeys do when aspirin is given during the course of experimentally induced fever (143). Whether this is a specific effect may be open to question, because the monkeys with lesions did not sweat under any of the conditions achieved in this experiment.

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## ENERGY METABOLISM

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This review is concerned with energy exchange principally, the rate of oxygen consumption being employed as an index of the expenditure of energy. A number of publications have appeared on effects of climatic conditions and the lack or abundance of vitamins in which either the energy expenditure was calculated or the oxygen consumption was measured during rest and muscular work. These, however, are not included as they more properly belong under other subjects than the one considered here.

### ENERGY INTAKE

In any discussion of the metabolism of energy, information on the energy intake properly belongs in it as well as measurements of energy expenditure. Several editorial reviews or articles have appeared on the calculation of energy content of the food intake and on dietary standards.

One editorial discussion (1) takes up the question of the calculation of the energy of the food from the Atwater caloric factors for proteins, fats, and carbohydrates in comparison with the English system. This problem applies more particularly to the carbohydrates in the diet. The Atwater factors were based on the normal distribution of the three nutrients as derived from a large number of dietary surveys in American groups and on the digestibility coefficients as derived from numerous digestibility studies. The English system is based on the "available" carbohydrates (starch and sugars) as actually determined by analysis of the foods used. In addition, the sugars, both reducing and hydrolyzable, are converted to starch by suitable factors and these amounts multiplied by a caloric factor. According to the author, these procedures result in caloric values that are too low because the determinations of starch and sugars do not give all the digestible substances usually included in the nitrogen-, ash-, and fat-free portion of the food and

\* This review covers the period from September 1944 to August 1945.



because the factor used for starch is too low. The Atwater system was based on a normal distribution of foods of animal and vegetable origin; however, some war-time diets have more foods of vegetable origin and the flour used is not of so high an extraction. To gain more exact information on the real fuel values of the ingested food it might be advisable to calculate the distribution between foods of animal and vegetable origin and then apply the suitable factors to these two classes of foods. This procedure would involve much work. It is pointed out that this whole question of the energy value of the food intake is of importance because of the necessity for some agreement in connection with food supply for the various national groups that need assistance in providing an adequate supply of food in the near future.

Another editorial review (2) also discusses the differences between the American and English methods of calculating the fuel value of dietary intakes. The attempts at refinement in such calculations, especially on the "availability" of natural carbohydrates, are critized and considered unwarranted, misleading, or inaccurate. Examples of the complexity of exact calculations of nutritional value are mentioned as exemplified by the problems of heat of hydrolysis of alcohol as a fuel, and on the differences in efficiency of fats and carbohydrates in muscular work. Too little is known about the efficiency of the different carbohydrates in relation to muscular work. An example is given of absurdities which occur in the calculations of energy value of diets in comparison with the actual findings on the nutritive conditions of school children. It is pointed out that revision of caloric tables to include "available carbohydrate" in the old sense may lead to a false sense of accuracy.

In a discussion of dietary standards (3) it is pointed out that the standards can only apply to groups as a whole rather than to individuals; that for some in the group the quantity of food supplied might be too large and for others too small; and that only by making the surplus available to those who need more would adequate nourishment be provided. That is, the surplus resulting from the lack of consumption by those who need less than the standard could be used in the distribution of food to those who need more. Much more information is needed on individual variations from the standard requirements in order to be able to apply the standards to individuals.



The effects of variations in activity, food intake, and environmental temperature were studied with twelve female albino rats in the age range of four to twelve months (4). There was a negative correlation between weight change and activity when food intake was constant. When the food intake was increased, there was an increase in body weight when activity and environmental temperature were constant. Weight gain was greater at 86° than at 70°F. when the food intake and activity were constant. It is suggested that the hypothalamus may be the level of the central nervous system responsible for control of energy exchanges.

*Dietary studies.*—The calorie intake of 203 American college women calculated from estimates of food consumption over a period of one week averaged 2,016 kcal. per day (5). The mean energy requirement as calculated from two-day activity records and the expected weight for age and height of 132 women was 2,285 kcal. per day. It is concluded from a comparison of the calculated energy requirement with the National Research Council standards of 2,500 and 2,100 for a fifty-six-kilogram woman, moderately active or sedentary, respectively, that college women should be classed as sedentary.

A dietary survey of twenty farm households at Ile Perrot, Quebec showed that the calorie intake was generally adequate (6). Approximately 50 per cent of the calories were from carbohydrate, 12 per cent from protein, and 39 per cent from fat. In the higher income brackets the calorie intake exceeded markedly the requirement. The protein, calcium, and iron intakes were reasonably adequate, but there were greater and more widely distributed deficiencies of thiamine, riboflavin, and ascorbic acid.

In a dietary survey of a week's duration in a convent in St. Anne de Bellevue, Quebec, with sixteen adults and forty-three girl boarders, it was found that the calorie intake was 81 per cent of the Canadian standard with a distribution of the calories as 37 per cent from fat, 51 per cent from carbohydrate, and 12 per cent from protein (7).

In a medical survey on 868 unselected people in St. John's and several outposts in Newfoundland, it was found that in the food available in Newfoundland there was an adequate supply in respect to calories and protein, but in spite of this, there were deficiencies in the mineral elements and vitamins (8).

## BASAL METABOLISM

The basal metabolic rate of thirty-seven medical students aged eighteen to twenty-five years, who underwent various tests for physical fitness and mental alertness averaged  $-5.9$  per cent and three to five days later,  $-6.3$  per cent (9). The authors conclude that medical students are below the average in B.M.R. or else that the standards are too high.

In a study of body size and amount of oxygen used in work simulating operation of an aeroplane (10), it was found with twenty-seven men that the largest man consumed 57.9 per cent more oxygen than the smallest man at rest and 62.8 per cent more at work. The correlation coefficient between the oxygen consumption and body surface was  $+0.76$  at rest and  $+0.82$  at work.

In a study with seven subjects who were nearly completely submerged in mineral water baths that contained a supersaturation of 30 to 34 per cent by volume of carbon dioxide, no effect on the oxygen absorption was observed in comparison with the oxygen absorption in plain water baths or in the baseline periods (11).

*Racial metabolism.*—In a review on racial metabolism from the standpoint of anthropology is listed the various investigations on the basal metabolism of races, and a discussion is given of the various factors which might explain the divergences in the conclusions drawn from racial studies (12). These are technique, functional normality, climate, diet, social milieu, degree of physical activity and muscular relaxation, body size and type, and normal standards. Because of the complexity of the problem and the lack of agreement at the present time in the interpretation of the findings in racial studies, it would be desirable to establish a standard for each race, based on measurements of normal individuals of the race in their native country. When such standards have been established for many different races, comparison of these with the American and European standards should measure the role played by race in basal metabolism.

*American Negro.*—A series of 182 basal metabolism determinations on twenty-seven healthy Negro women between seventeen and thirty-five years of age was made, as well as thirty determinations on fourteen Negro men between eighteen and twenty-four

years (13). The women averaged 14.8 per cent and the men 12.44 per cent below the Boothby and Sandiford modification of the DuBois standards. In confirmation of earlier work a premenstrual rise with a lowering during the actual menstruation and in the immediately following postmenstrual period was found.

*Human pregnancy.*—The basal metabolic rate of 163 women was followed during gestation and particularly in the last month of pregnancy (14). The weight, length, and skeletal development of the infants were recorded at birth and at one, three, and six months of age. Infants of mothers with a high metabolic rate during the ninth month were heavier and longer at birth and more advanced skeletally at one month than the infants of mothers with low metabolic rates during the last month of pregnancy. The correlation coefficient between the basal metabolism at the ninth month and the gain in basal metabolism during pregnancy was  $+0.68$ .

In another series of determinations by the same group of workers (15), of the changes in basal metabolism of women during pregnancy it was found that in 158 women, those with the lowest nonpregnant basal rates tended to have the greatest gains in rate during pregnancy. The correlation coefficient in this group between the pregnancy basal gain and the nonpregnant basals was  $-0.62$ .

*Rats and mice.*—The effect of food on the critical temperature for the albino rat was determined on six rats in comparison with the critical temperature for the same rats in the fasting condition at temperatures from  $15^{\circ}$  to  $34^{\circ}\text{C}$ . (16). The zone of thermal neutrality for fasting rats was from  $28^{\circ}$  to  $33^{\circ}\text{C}$ . Food lowered both limits by  $1^{\circ}\text{C}$ . About one-third of the heat increment due to food was manifest below the critical temperature.

Ovariectomy at twenty-six days of age increased growth rate and basal metabolic rate in the albino rat (17).

The basal metabolism of pregnant rats was measured on the thirteenth and twentieth day of pregnancy on normal rats and on rats precociously sex-matured by injection of equine gonadotropin (18). Virgin rats were used as controls. On the thirteenth day the metabolic rate per unit weight of normal rats was increased 16 per cent. In the precocious rats it was only 5 per cent. On the twentieth day the normal rats had an increase of only 9 per cent over the virgin rats.

Weanling mice were fed on a diet restricted in cystine to effect retardation in growth (19). To determine whether the resulting undernutrition lowered the basal metabolism, the oxygen consumption was determined on this group and on a group fed the same diet supplemented by cystine for three to fifteen months. No essential differences were found.

*Poultry.*—The basal metabolic rate of forty white leghorn hens in summer and winter averaged 400 to 500 cc. oxygen per kg. per hr. before and after molting and 600 to 700 cc. during molting (20). Oral administration of Lugol's solution or diethylstilbestrol had no effect on the course of molting.

#### ENDOCRINES

No effect of large doses of adrenal cortex on the rate of oxygen consumption during work was found when given to healthy young men who lived on a constant diet and marched for three and one-half hours daily in moist heat (21).

The injection of 0.0366 to 1.666  $\mu$ g. per kg. per min. of epinephrine in chloralosed dogs resulted in an increase in the respiratory exchange of 3 to 12 per cent (22). The subcutaneous injection of 0.1 to 0.5 mg. in men resulted in an increase in the respiratory exchange of 8.9 to 57.2 per cent.

#### DRUGS

*Atabrine.*—The effect of atabrine on the oxygen consumption of tissues was determined on rat liver, kidney, and brain tissues (23). At first there was a slight rise followed by a marked fall, particularly with liver and brain. After such inhibition the tissues were unable to oxidize glucose, lactate, pyruvate, malate, citrate, or fumarate, but could oxidize succinate with oxygen equivalent to a conversion to fumarate. The indications were that atabrine interfered with the yellow enzyme system.

*Thiouracil.*—In twenty-five young adult albino rats the maximum depression in basal metabolism was 19 per cent and the average 10 per cent after twenty days of feeding Purina diet with about 0.5 per cent admixture of thiouracil (24). No further decrease was found during sixty days of feeding.

The relation between the effects of graded doses of thyroxine on metabolism and the thyroid weight of rats treated with thioura-

cil was established with male albino rats (25). The metabolism was depressed 23 per cent and the thyroid weight more than doubled in rats treated with 0.1 per cent thiouracil in drinking water for fourteen days. The metabolic rate was returned to normal by the daily injection of 4.75  $\mu$ g. of *dl*-thyroxine. The authors believe that thyroid assays or measurements of thyroid function, determined by the thiouracil technique, are directly comparable with results obtained by basal metabolism measurements.

Groups of rats were either thyroidectomized or treated with thiouracil, and their individual metabolisms were measured until they reached a constant level; this took about six weeks (26). They were then subjected to thyroid medication. The rats treated with thiouracil showed a slower decline in metabolic rate than did the thyroidectomized rats but ultimately attained the same level as the operated animals. The individual variations in the thiouracil-treated rats were considerably larger than in the thyroidectomized animals, and their responses to ingestion of standard doses of thyroid substances were erratic and irregular.

A number of publications have appeared on the use of thiouracil in the treatment clinically of thyrotoxicosis and hyperthyroidism and the preparation of patients for thyroidectomy in which the basal metabolism has usually fallen during treatment with the drug (27 to 33).

#### ORGANS AND TISSUES

*Brain.*—Determinations of the oxygen uptake with and without added lactate, lactate removal, and oxidation quotient of lactic acid were made on finely minced cerebrum and brain stem of normal and thiamine-avitaminotic chickens (34). In the avitaminotic brain the increased oxygen uptake with added lactate was only 36 per cent of that of normal brain studied. No differences were found between normal and avitaminotic cerebrum.

The cerebral oxygen absorption was measured in twenty-six experiments on Indian rhesus and spider monkeys *in vivo* in lightly anesthetized animals by measuring cerebral blood flow directly while samples of cerebral venous and arterial blood were collected for subsequent analysis (35). The "normal" mean  $Q_{O_2}$  was 11.1, the "normal" minimum was 7.5 and the "normal" maximum was 13.5.

*Eye muscle.*—The  $Q_{O_2}$  of the normal eye muscle of the guinea pig was found to be 87.5 per cent higher than that of the diaphragm and 187.5 per cent higher than that of the latissimus dorsi muscle of the same animals (36). Injection of thyroxine affected the  $Q_{O_2}$  of all three muscles. The least effect was on the eye muscles. Thyroid ablation led to a marked but differential decrease in the  $Q_{O_2}$  of all muscles. It is suggested that the enzyme systems, which are the sites of action of the thyroid hormone, are present in variable amounts or are more active in different muscle tissues.

*Thyroid.*—The oxygen consumption of thyroid tissue from guinea pigs was measured by the Warburg technique at 5°, 38°, and 40°C. The tissues were then examined histologically in comparison with control portions of the same lobes of the same glands (37). In the tissues with high  $Q_{O_2}$  due to temperature, the follicular cell height was relatively low. Conversely, low  $Q_{O_2}$  was usually associated with an increased cell height. It was suggested that this change may be due to an indirect effect of thyrotropic hormone.

*Various tissues.*—In confirmation of earlier workers it was found that the rate of respiration of various mammalian tissues (rabbit bone marrow and kidney cortex, rat liver and kidney cortex, and guinea pig liver) was 20 to 40 per cent higher in Ringer-bicarbonate- $CO_2$  medium than in Ringer-phosphate medium (38).

The  $Q_{O_2}$  of cerebral cortex, diaphragm, kidney cortex, and liver of rats poisoned with arsenic trioxide was determined in comparison with the  $Q_{O_2}$  of the same tissues in normal animals (39). When the drug was administered subcutaneously *in vivo*, there was no effect on cerebral cortex respiration, a reduction of diaphragm and kidney respiration, and a stimulation of liver respiration. When the drug was given intraperitoneally *in vivo*, there was no effect on the cerebral cortex respiration but a reduction in the respiration of the other tissues. The authors conclude that the hypothermia of arsenic poisoning is influenced more by a decreased rate of energy metabolism of the individual tissues than by a direct effect on the temperature regulating center in the nervous system.

The oxygen consumption of rat liver slices has been shown to be increased in lymph collected from the hind legs of a dog when this area has been burned in comparison with the oxygen consumption of the rat liver slices in normal lymph from the same area (40). Similar results were obtained on the oxygen consumption of rat diaphragm muscle.

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## RESPIRATION\*

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The literature of the past year on respiration reflects the attention paid to problems of the war effort. The majority of published articles deals with amelioration of the effects of anoxic anoxia. More significant have been the contributions in the field of gas exchange. This branch of respiratory physiology has been markedly stimulated by the need of aviators for better systems of oxygen supply, the hazards of decompression sickness, and the dangers of carbon monoxide and other toxic gases. The practical success of some of these war-time investigations can be judged by the fact that oxygen equipment is now in use which will maintain a man with adequate oxygenation at altitudes of 43,000 feet (1).

### GAS EXCHANGE

Important constants for the dynamics of gas exchange in the lungs of normal men have been furnished by Roughton (2). He found the time of transit of blood through the pulmonary capillaries to be  $0.75 \pm 0.25$  sec. at rest and  $0.34 \pm 0.1$  sec. during heavy exercise. The amount of blood contained in the capillaries under the two conditions was 60 and 95 cc. respectively. The calculations essential for obtaining these quantities involved, among other things, the possession of accurate data on the rate of carbon monoxide uptake (3) and the kinetics of the reaction,  $\text{CO} + \text{O}_2\text{Hb} \rightleftharpoons \text{O}_2 + \text{COHb}$  (4). Despite the rapidity with which blood is flowing through the lungs, the demonstration that arterial blood is 98 per cent saturated with oxygen (5, 6) and has a partial pressure of oxygen (97.1 mm. Hg) in substantial agreement with its partial pressure in alveolar air (7) clearly indicates that diffusion of oxygen through the alveolar and capillary membranes is not a limiting factor in gas exchange under normal conditions. Under pathological conditions the situation is not so clear. Samples of air from the two lungs (8), particularly in tuberculosis (9), often show a difference in composition. In patients with silicosis (10) a drop in arterial

\* This review covers the period from July 1944 to July 1945.

saturation may occur with mild exercise. While diffusion through the alveolar membranes may be impeded in these instances, it is also probable that a factor concerned is the rate of renewal of air at the alveolar surfaces since constriction of the air passageways would greatly affect the mixing time in the lungs.

Oxygen utilization by the brain *in vivo* has previously been estimated from arterial-venous differences in oxygen concentration. For example, Blalock (11) by means of this method has studied oxygen utilization in traumatic shock. Development of a reliable method of blood flow by Schmidt *et al.* (12), and its application to man by Kety & Schmidt (13), remove the ambiguity usually present in the interpretation of arterial-venous differences. They find in the monkey that cerebral oxygen uptake is more closely correlated with blood flow than with the actual arterial-venous difference. The measurements made by Bronk and co-workers (14) on partial pressure gradients of oxygen in cerebral tissue show that the major factor controlling the oxygen pressure in a given region is the distance from the nearest capillaries. The quantity of blood flowing through the tissue capillaries still remains as the major factor conditioning gas exchange in the tissues. The partially collapsed lung (15) following pneumothorax has a decreased oxygen uptake, minute volume, and tidal air, for which the normal lung compensates. A review with numerous references on emphysema has been assembled by Macklin & Macklin (16).

Morales & Smith (17 to 20) have developed a general theory of blood tissue gas exchange. The total uptake of a gas is given as a function of the arterial concentration, the cardiac delivery, the blood volume, and the volume, permeability, and partition coefficient of each tissue. Applications of the theory to the lungs, to circulation through the tissues, and to the determination of specific tissue constants are discussed. They indicate that the Fick principle is merely an approximation of a more general equation with which it should be possible to determine the functional lung surface in the case of a slowly permeating gas.

*Bubble formation.*—The problems of decompression sickness have led to detailed and extensive investigations into the factors affecting bubble formation and growth of bubbles in aqueous solutions (21). Harvey and co-workers (22 to 27) have clarified the situation for animal tissues by means of an excellent theoretical analysis and a series of beautifully planned experiments. Whitaker,

Blinks, and co-workers (28 to 31) have made extensive investigations of the factors facilitating bubble formation. Bubble formation can occur whenever the partial pressures of the dissolved gases exceed the local hydrostatic pressure by a definite amount. The process of bubble formation is facilitated by the presence of bubble nuclei, or by turbulence which results in greatly reduced or even negative hydrostatic pressures (tension). Thus, during exercise, the mechanical factors appear to be more important than metabolic factors which lead to local increases in partial pressure of carbon dioxide. Elimination of nitrogen from the tissues greatly reduces the incidence of bubble formation, since under most experimental conditions nitrogen dissolved in the body tissues is the gas which is present at the highest partial pressure. Because of the high solubility of nitrogen in the fatty tissues, bubbles appear in tissues rich in lipids (32). They occur in blood vessels (32, 33), and most frequently in those tissues with a poor blood supply (34).

#### ANOXIA

The great variability observed in experiments dealing with anoxia indicates that many factors affecting the response to anoxia are as yet dimly understood. If the stress is made great enough, the variability from subject to subject may be reduced. Human subjects develop increased heart rates, elevated blood pressures, and increased respiratory rates if allowed to breathe gas mixtures containing 2 to 3 per cent of oxygen (35). At altitudes below 26,000 feet, subjects may show unusual resistance to the effects of anoxia, but above 26,000 feet the period of useful consciousness is five minutes or less, and decreases in a regular fashion with altitude (36). At 35,000 feet the period of useful consciousness is reduced to seventy seconds (37). The most sensitive functional index of anoxia so far studied is visual threshold. The differential visual threshold has been found to be adversely affected even below altitudes of 5000 feet (38, 39).

*Chemical changes in the body fluids and tissues.*—During mild anoxic anoxia, the pH of the arterial blood shifts in an alkaline direction, rapidly returning to normal values when the anoxia is relieved (40, 41). A decrease in the inorganic phosphate level of the blood occurs in both animals and man (42, 43, 44), and as a consequence a decreased excretion of inorganic phosphate occurs in the urine. The changes in tissue electrolytes (45), and in the

urinary excretion of sodium, potassium, chloride, nitrogen, and 17-ketosteroids at altitudes up to 18,000 feet are not marked (46). The small differences observed may be due to minor changes in urine volume (47). At higher altitudes there may be a reduction in urinary secretion and in chloride secretion, effects which may be delayed until the altitude of 24,000 feet is reached (48) if the kidneys are denervated. Epinephrine appears to be the stimulus for the modification in the urine observed above 24,000 feet. The blood levels of lactic acid and pyruvic acid are only slightly increased by exposure to simulated altitudes ranging from 15,000 to 18,000 feet (49).

Studies of the adrenals have shown a reduction in the lipid content of the gland after a single exposure to anoxia (50). The cholesterol content of the gland falls from 3.4 per cent to 1.8 per cent after a short stay at barometric pressures of 200 to 300 mm. Hg. Recovery is apparently complete in eighteen hours (51). The realization of the fact that adrenal cholesterol is an active substance and probably participates in many reactions promises to furnish new insight into adrenal function under conditions of stress (52). The increase in size of the adrenals on exposure to a barometric pressure of 225 mm. Hg for seven hours is thought to be due to a hyperemia resulting from hyperactivity; after twenty-four hours exposure there was exhaustion atrophy as evidenced by histological study (53). In contrast to the adrenals, the liver responds to anoxia with the deposition of fat (54).

There is no evidence that residence at high altitudes will increase the affinity of hemoglobin for oxygen. In fact, there may be a slight decrease, representing perhaps a compensatory adjustment to the low pressure environment (55). The rise in hemoglobin concentration seen in the blood as a result of anoxic anoxia is duplicated at times by exposure to carbon monoxide anoxia. The rise following exposure to carbon monoxide is a late response, and may occur several days after the exposure (56).

Anoxia speeds the development of hypovitaminosis-C in guinea pigs (57). Rats exposed to an altitude of approximately 25,000 feet, three hours a day for twenty-five days, showed evidence of disturbed calcification of the teeth (58). Tissues of animals examined by the Warburg technique after death from anoxic anoxia showed a decreased oxygen consumption for liver and heart tissue, while kidney, skeletal muscle, and cerebral cortex were unaffected

(59). Very severe anoxic anoxia may slightly delay absorption of ingested fat, while mild anoxia is without effect (60).

*Effects on the nervous system.*—In the opinion of Hoff *et al.* (61) there is a remarkable similarity in the pathology of the nervous system produced by anoxia, hypoglycemia, carbon monoxide poisoning, circulatory arrest, anaesthetics, etc. They believe the "common mechanism" underlying the production of the lesions is both vascular and metabolic. A clear-cut demonstration that multisynaptic cord reflexes are less resistant to anoxia than the nonsynaptic reflexes has been presented by Van Harreveld (62). The experiments of Alexander (63) are of interest. He found that the "isolated" spinal cardiovascular centers respond to reduced oxygen pressure with an increase in activity. This is in contrast to other centers, as for example the respiratory centers, in which anoxia appears to depress activity (64, 65). The "tone" of the third cranial nerve is also thought to diminish with anoxia (66). The stimulated portion of nerve seems to be more sensitive to anoxia than the purely conducting region (67). In man, the apprehension of stimulation produced by alternating currents of 15,000 to 30,000 cycles diminishes with anoxia (68). Whether this is a peripheral or a central effect is unknown. It is now quite clear that cerebrospinal fluid pressure is not increased by decompression unless anoxia sufficient to raise the blood pressure is encountered (69, 70).

*Respiration and circulation.*—The changes in the composition of alveolar air occurring with reduced barometric pressures have been well established (71), and these studies have also yielded figures for the increased cardiac output that occurs with anoxia. An increase in cardiac output of 200 per cent may occur at 20,000 feet, thus partially compensating for the reduced alveolar oxygen pressure (72). The discrepancy between the end inspiratory and end expiratory respiratory quotients is much diminished by anoxia, and Haldane's hypothesis of a different dead space for oxygen and carbon dioxide does not appear to be valid (73). An investigation of the effects of altitude upon subjects with pneumothorax has shown that subjects with a 50 per cent collapse of the lung develop marked symptoms at 15,000 feet (74). After a period of anoxia, inhalation of adequate oxygen can lead to a period of apnea (75); in general, however, respiratory and cardiovascular disturbances are more profound if the anoxia is slowly relieved (76). An interesting consequence of anoxia is the increased expiratory

volume of the chest reported by Harris (77), which in cats may amount to about three times the tidal air. Vagotomy greatly reduces the rise in cats, and completely eliminates it in dogs.

The hypertension produced by anoxic anoxia in the systemic circulation (78) is paralleled by an increase in the blood pressure of the pulmonary circulation (79). If the venous oxygen pressure falls below 20 to 30 mm. Hg blood flow increases rapidly, due in part to vasodilation (80) resulting from a small decrease in the oxygen partial pressure of the venous blood. A much larger decrease in arterial oxygen pressure may be without effect. The electrocardiographic changes in anoxia are in part due to a mechanical rotation of the heart which results from the increased respiratory effort (81, 82). The flattening of the T-wave cannot be reproduced by excessive inflation of the chest, and is probably a result of the dilation of the heart under the increased cardiac load. Residents of high altitudes have an increase in the transverse diameter and the frontal areas of the heart of 11 and 16 per cent respectively (83), probably one of the many compensatory effects of reduced oxygen pressure. Carbon monoxide produces heart lesions in dogs at levels considered safe for men (84, 85). Whether this is due to greater sensitivity of the dog to carbon monoxide is unknown.

Hypocapnic anoxia decreases intestinal motility (86, 87, 88). The effect is mediated reflexly through the central nervous system in mild anoxia. In severe anoxia this is both a direct effect on the organ, and an effect due to epinephrine. Hypercapnic anoxia, in contrast, may increase intestinal motility. The decreased motility due to anaesthetics is enhanced by anoxia (89, 90).

*Amelioration of anoxic signs.*—Impairment of subjective sensory functions in anoxia was found to be closely correlated with the appearance of the electroencephalogram, and these changes could be largely offset by the addition of 3 per cent carbon dioxide to the breathing mixture (91). Garasenko (92) finds that carbon dioxide markedly improves the feeling of well being and the capacity to do work at high altitudes. The increased excitability of the cerebral cortex observed in moderate hypoxemia (93) is reversed by increasing the carbon dioxide pressure (94, 95), although carbon dioxide does not modify the effects of a severe hypoxemia. The effect of carbon dioxide on conditions of mild anoxia is largely unexplained, but it is interesting that in the presence of Ringer-

carbonate media tissues show an increased tissue respiration over that in Ringer-phosphate media (96). The time of survival of the primitive respiratory centers of rats correlates roughly with the blood sugar level up to concentrations of 180 mg. per cent (97). Both adrenocorticotrophic hormone (98) and adrenal cortical extract (99) increase the survival time of rats at high altitudes, while 17-hydroxycorticosterone and sodium succinate are without effect. The adrenal hypertrophy produced by anoxia can be prevented if the exposure is conducted with sufficient carbon dioxide in the air breathed (100). It is suggested that the adrenals respond to the disturbed acid-base balance which accompanies the anoxia, and not to the low oxygen pressure directly. The survival time of rats exposed to low barometric pressures is increased by thiouracil, thiourea, and other agents which inhibit thyroid function and reduce the metabolic rate (101 to 104). The primitive respiratory center of the rat withstands anoxia better in the presence of sulfanilamide or sodium sulfathiazole (105), while other sulfonamides are without effect. Some of the factors affecting resistance to anoxia in mice have been discussed by Hiestand & Miller (106), and by Kibrick & Goldfarb (107). Starvation, dehydration, food intake, and rate of ascent are significant variables in experiments testing the response of animals to anoxia. In man, morphine (108), pavatrine (109), and sulfathiazole (110) in therapeutic doses are without effect on resistance to anoxia, and it is concluded that such drugs may safely be used when transporting battle casualties by air.

Despite the many attempts to increase tolerance to anoxia, the only practical method developed so far which can be employed by aviators is the ingestion of a high carbohydrate diet (111). By this means a small but definite increase in altitude tolerance has been obtained. If blood sugar levels are low, the tolerance to anoxia is decreased (112). For aviators, the problem of anoxic anoxia is largely solved by the excellent oxygen equipment now available (113).

#### OXYGEN TOXICITY

Inhalation of oxygen at a pressure of one atmosphere produces symptoms of lung irritation in normal young men after about fourteen hours exposure (114, 115). Symptoms of substernal distress



were produced in 55 per cent of the subjects after a twenty-four hour exposure to oxygen at a pressure of three-fourths of one atmosphere. Bean (116) believes that the adverse effects of high oxygen pressures are produced through interference with enzyme systems of the cell, with consequent production of cellular anoxia and acidity. Oxygen toxicity produces both acute and chronic effects in the central nervous system, with the appearance of easily demonstrable lesions (117, 118). During the acute stages, the electrical activity of the cerebral cortex is similar to that observed in other convulsive disorders (119). The poisoning effect of high pressures of oxygen is related to the metabolic state of the animal. Hyperthyroidism increases the sensitivity of cats to high oxygen pressures, while hypothyroidism decreases sensitivity (120). Mammalian smooth muscle responds to increased oxygen pressure with a decrease in tonus, but is unaffected if first treated with sodium cyanide in concentrations which inactivate the cytochrome oxidase system (121). Tissue respiration is more than doubled at five atmospheres pressure of oxygen (122). In contrast to the increase in erythrocytogenesis observed with low oxygen pressures, high oxygen pressures decrease erythrocytogenesis (123). In animal experiments, both temperature and humidity may affect the response to increased oxygen pressures (124). The animals do better at normal temperatures and moderate humidities than at high temperatures or high or low humidities. Monkeys are more resistant to 90 per cent oxygen than rabbits (125), illustrating the wide species variability in susceptibility to oxygen poisoning. Rats, exposed for short periods to increasing pressures of oxygen, may develop a tolerance to 100 per cent oxygen (126).

#### CONTROL OF RESPIRATION

Gesell & Hansen (127) have advanced further arguments in favor of the acid-humero-electrotonic theory of the mediation of nerve impulses. The conclusion is drawn that carbon dioxide does not stimulate the respiratory center directly, but indirectly determines the effectiveness of presynaptic volleys through control of acidity and the rate of breakdown of acetylcholine. The inspiratory center in the rabbit has been found by Wyss & Crosier (128) to be situated at the level of the hypoglossal nerve. The effects of anoxia or respiration are mediated reflexly through the



carotid glomus (129), and the carotid chemoreceptors are much more sensitive to respiratory stimulating agents such as lobeline than are the cardio-aortic receptors (130). Doubt has been cast by Hollinshead & Sawyer (131) on the theory that the chemoreceptors of the carotid body are aroused to activity by the release of cholinergic substances. They found the cholinesterase level of the carotid body to be extremely low. Mills (132) has examined the hyperpnea produced in man by the sudden release of occluded blood, and he concludes from the latency measurements on lung circulation time that the respiratory response is due to pressure receptors in the pulmonary vascular bed. Other experiments involving the hyperpnea of sudden muscular effort (133) yielded results which indicate a pronounced cortical factor in the respiratory response obtained.

Grandjean (134), in an analysis of the effects of stimulating the central end of the cut phrenic nerve, indicates that the phrenic nerve carries only pain impulses, and is without any specific regulatory function. The vagal stretch endings in the lungs show no change in frequency of discharge under conditions of experimental congestion (135), and doubt is therefore cast on the current hypothesis evoked to explain cardiac dyspnea. In patients with an obstructed superior vena cava, tissue stasis in the brain and hyperventilation of cerebral origin may account for the altered chemical relationships in the blood (136). It is interesting that the respiration of lizards (137) and snakes (138) is controlled by oxygen, and in both species carbon dioxide depresses respiration.

*Effect of drugs.*—Picrotoxin enhances the electrical excitability of the respiratory center of cats (139). Alpha and beta nicotine injected into the carotid artery give a transient stimulation of respiration, the beta nicotine compound being the more powerful. The stimulating effect is by way of the carotid body (140). Hyperventilation usually abolishes the reflex effects of nicotine and cyanide in anaesthetized dogs by reducing the sensitivity of the respiratory center to afferent impulses (141). Isobornine stimulates respiration reflexly, though it may also have some central action (142). The allyl compound of morphine will prevent the depression of respiration brought about by morphine (143). Privine may act synergistically with sodium pentobarbital in depressing respiration (144).

*Miscellaneous reports.*—In experimental traumatic shock, death occurs as a result of a sudden or progressive failure of the respiratory center. The period of failure is often preceded by one of respiratory stimulation (145). Therapeutic baths containing high concentrations of carbon dioxide raise the alveolar carbon dioxide pressure, apparently because of the absorption of appreciable quantities of carbon dioxide through the skin (146). The narcotic properties of high concentrations of carbon dioxide have been studied by SeEVERS (147), who finds that in a high percentage of cases among rats exposed to 20 per cent carbon dioxide in air, death will result, while 15 per cent carbon dioxide mixtures produce a prolonged decrease in oxygen consumption. The lungs are damaged by breathing heated air only when the temperature is high enough to produce instantaneous burning of the skin and upper respiratory passages. The larynx must be protected in order to produce the lesions of thermal pneumonitis (148).

SCHMIDT (149) has outlined the newer concepts of respiratory physiology and their relation to the problems of anaesthesia, and DRINKER (150) has discussed the physiology of respiration with respect to oxygen therapy. The hemoglobin concentrations of young college women have been determined (151). The mean value found was 13.4 gm. of hemoglobin per 100 cc. of blood; the mean erythrocyte count was found to be 4.5 million. DRABKIN (152) has studied the crystallographic and optical properties of human hemoglobin and has proposed a hemoglobin standard based upon the nitrogen value of a salt-free solution of crystalline hemoglobin.

#### METHODS

A simplified photoelectric colorimeter has been described for determination of derivatives of hemoglobin in blood (153). The instrument makes use of absorption spectra in the near infra red. Hemoglobin in the tissues can be determined as acid hematin after repeated extraction of the tissues (154). A new colorimetric method for the determination of blood oxygen has been developed (155) which gives results in good agreement with the standard method of Van Slyke & Neill (155a). Blood equalling in oxygen content the arterial blood can be obtained from the heated ear (156). The Milikan oximeter (157) with automatic compensation for ear thickness has been checked against data obtained from chemical analy-

sis of arterial blood. Agreement within  $\pm 5$  per cent of the arterial saturation for values of oxygen as low as 60 per cent saturation were obtained (158). Synthetic detergents of the long chain alcohol type, the alkyl aryl sulfate, or the monoglyceride sulfate type are useful hemolytic agents in the standard procedures for the determination of blood oxygen capacity (159). An improved method for the determination of carbon monoxide in air and in other gases with the Van Slyke apparatus has also been developed (160).

A simple ventilation recorder for small animals has been described by Little (161), in which he makes use of a standard metabolism apparatus. The small valves developed for oxygen masks can be used in making a respiration recorder for small animals (162). A convenient manometric device for respiratory studies on small animals has been described (163). An ingenious method for determining the velocity of air movement by means of the deflection produced in small wires has been published by Silverman *et al.* with which total minute volume and instantaneous air flow can easily be obtained (164). The increasing use of radioactive gases in respiratory studies has been facilitated by the development of Geiger counters suitable for continuous study of mixtures of respiratory gases (165). An improved method for continuously following the oxygen consumption and carbon dioxide production has been used to demonstrate increased oxygen and carbon dioxide exchange following injection of epinephrine (166). The tidal air of laboratory animals in the basal state has been found to be equal in liters to 212 times the body weight in kilograms raised to the three-fourths power (167). The vital capacity in man is more accurately and easily obtained by means of the spirometer method (168) than indirectly, as advocated by Goadby from external measurements on the trunk (169).

*Resuscitation.*—The Eve rocking method of artificial resuscitation (170 to 176) has been found to be one of the best methods for the ventilation of the lungs in an apneic individual. The procedure can be carried out with a minimum of training, its only disadvantage being the fact that it requires either a suitable apparatus or else more than one person to use the method. The "pole top method" of artificial respiration may be useful in crowded situations such as on a life raft (177). The need for increased rates

when using Schäfer's method in cases of asphyxia has been emphasized by Tingley (178), and the need for correct timing in Schäfer's method (178a) has been reaffirmed by McMaster (179).

Suitable mechanical resuscitators can be much more efficient than manual methods (180 to 183), and if available are more adaptable for use in a variety of conditions. A study of various mechanical resuscitators demonstrated little effect on pulmonary blood pressures; however, if positive pressures greater than 10 to 12 mm. Hg are applied for prolonged periods, there may be serious interference with the venous return to the heart (184).

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## THE PHYSIOLOGY OF THE SKIN

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This review covers the literature of the period from September 1943 to September 1945. In selecting the material we have set the same limitations as was done in a previous review (1) in order to avoid overlapping with chapters on the physiology of special senses, on effects of cold and heat, and on radiation effects. Only a very few foreign language publications were available but we had access to a review of European publications on physiology of the skin by Lutz (2, 3).

### NUTRITIONAL FACTORS

Severe, nonspecific cutaneous disorders due to nutritional deficiencies have been reported in numerous publications, most of which deal with the withdrawal of single B-factors.

*Riboflavin.*—In riboflavin deficiency of swine a mottled erythematous eruption, ulcerations, crusting, scaling, and anomalies of hair growth and of growth of horns and hoofs were found (4). Similarly in monkeys riboflavin deficiency resulted in mottled dermatitis, which in severe cases became crusty and oozing (5). In albino mice similar changes were observed (6). In these animal experiments no cheilosis and no vascularization of the cornea were noted. In man, Keys *et al.* (7) did not succeed in producing cutaneous or mucous membrane lesions in persons who were kept on a diet restricted in riboflavin to 0.99 mg. per day for a period of 152 days. Neither did Roth *et al.* (8) find pathological cutaneous or mucous membrane changes in adult healthy women who were kept on a diet restricted in riboflavin to 0.7 mg. per day over a period of 288 days. Nevertheless, clinical experience clearly indicates that riboflavin deficiency may result in inflammatory diseases of the mucous membranes of man. Stomatitis was observed by Jones *et al.* (9) in a North African camp, when riboflavin was cut to 1 mg. per day in the diet of soldiers. The stomatitis could not be cured by increasing the daily intake to 1.28 mg. for a month. Cure resulted, however, in five days when 100 mg. riboflavin were administered daily. In spontaneous vitamin deficiencies observed in the Federated Malay States (10) angular stomatitis also could be

checked by administration of either riboflavin or of vitamin B complex.<sup>1</sup>

*Pantothenic acid.*—The tegument of the cotton rat proved to be more sensitive to low pantothenic acid intake than to deficiency in any other B factor. Elvehjem *et al.* (11) found in pantothenic acid deficiency severe dermatitis with crusting, cracking, and open sores, resulting in death within six weeks, whereas no cutaneous changes were produced with diets low in thiamine, in riboflavin, in pyridoxine or in nicotinic acid. Also in swine, pantothenic acid was found to be an essential factor for the maintenance of physiological conditions in the skin (12). The coats of the deficiently fed swine became rough, and the hair appeared unkempt as early as three weeks after the diet had been started. Later the hair, mainly on the trunk, thinned and fell out. In some cases a patchy alopecia developed. The skin became red and scaly and severe ulcerating lesions of the tongue appeared. Dogs' skin seems to be less susceptible to pantothenic acid deficiency. In Silber's experiments (13) continued for two months, no cutaneous or mucous membrane lesions were observed; still, the hair of the experimental dogs was coarser than that of the controls. In mice a dry scaly skin developed together with loss of hair (6). It is noteworthy that in all these experiments no graying of the hair was noted as a symptom of pantothenic acid deficiency.

*Biotin.*—Severe scaly dermatitis was observed in acute biotin deficiency of monkeys, whereas in chronic experiments only thinning of the fur and gradual loss of hair pigment occurred (14). Accompanying the dermatitis there was a "rusty" appearance of the skin (15) which might have been due to the deposition of the porphyrin-like compound found in the "bloody tears" of pantothenic acid-deficient rats (1). The effect of biotin deficiency on hair growth was again demonstrated in mice (16) when rough fur coat, loss of hair, and finally typical alopecia were produced by this deficiency in four weeks and cured by addition of biotin. In monkeys, the hair loss was affected by hormonal influences as indicated by slower regrowth of the fur in menstruating and adolescent females (14).

*Nicotinic acid.*—The view that canine blacktongue as well as

<sup>1</sup> The greater vulnerability of mucocutaneous junctions and the lesser susceptibility of the skin in man, as compared with laboratory animals, to riboflavin deficiency was pointed out in an earlier review (1).

human pellagra are simply syndromes of nicotinic acid deficiency has met further challenge. Krehl & Elvehjem (17) found that healing of canine blacktongue by addition of nicotinic acid to the diet is appreciably facilitated if the basic diet contains folic acid. More than that, evidence is accumulating that human pellagra, particularly the infantile form with extensive fatty changes in the liver, cannot be cured by vitamin therapy of any kind but, on the contrary, vitamin therapy seriously aggravates this condition. Gillman & Gillman (18), who made extended studies on nearly 300 infantile pellagrins in South Africa and followed the condition of the fatty liver by serial liver biopsies, reported that all children treated with vitamins became rapidly worse and died. The condition was fairly improved by the administration of liver extract rich in the Cohn fraction, and dramatic improvement was obtained from administration of dry stomach. Sydenstricker *et al.* (19) kept two subjects, previously pellagra patients, on a diet containing a daily dose of 3 mg. of nicotinic acid. There was not any significant change which would have indicated recurrence of pellagra. The authors suggested that the 3 mg. dose is somewhere near the minimal human requirement of nicotinic acid.

*Other B-factors.*—It has been known that animals on a synthetic diet supplemented by all hitherto known accessory food factors may develop a dermatitis, so that unknown dietary factors must be postulated for the maintenance of normal functions of the skin. This postulate was substantiated by Elvehjem *et al.* (20), who demonstrated that a water-soluble material, called vitamin B<sub>10</sub>, contained in the liver concentrate "Super Filtrol eluate" (21), distinct from folic acid, is necessary for proper feather formation. The absence of the B<sub>6</sub> factor from the diet also was shown to cause retardation of feathering in the chick (22).

The work of Novak & Bergheim (23) indicates that B-factors are excreted with the growing hair. Riboflavin, nicotinic acid, pantothenic acid, and inositol were present in normal human and rat hair in about the same ratio to each other as in other tissues, the amount depending upon the rate of vitamin intake. It was emphasized that the finding of low inositol values in hair of balding men needs further investigation. Paul *et al.* (24) estimated the thiamine content of skin in adult rats to have an average normal value of 0.57  $\mu$ g. per gm. tissue. In healing cutaneous wounds the thiamine content was about twice as much.

*Ascorbic acid.*—In chronic ascorbic acid deficiency in rhesus monkeys Elvehjem *et al.* (25) observed, in addition to scurvy, loss of hair and a mild dermatitis. These cutaneous changes disappeared on administration of biotin. The much criticized method of Rotter, estimating ascorbic acid content of the tissues by intradermal injection of a dichlorophenol indophenol solution and by measuring the decolorization time of the dye in the skin, was found by Slobody (26) to be a reliable indicator of body saturation with vitamin C.

*Fat.*—White *et al.* (27) demonstrated the effect of diets devoid of fat on the skin of albino mice. A widespread scaly dermatitis appeared in these animals, and was easily cured by addition of lard. Anthony *et al.* (28) produced "rat acrodynia" by fat-deficient diet and assayed twenty-four seed oils for their potency in the cure. The potency was in direct proportion to the linoleic acid content of the seeds, whereas the presence of linolenic acid and other lipids reduced the curative effect. Without linolenic acid intake, 12 mg. of linoleic acid daily were found to be curative in acrodynia. Experiments of Hansen & Wiese (29) indicate that local cutaneous irritants such as croton oil have markedly increased irritating effects on the skin of dogs which receive low fat diets, as compared with dogs obtaining additional lard. There was a decrease in the iodine number of serum fats in animals on a low fat diet but the iodine number of skin fat did not show any change.

*Vitamin A.*—The hyperproduction of keratin in the follicular orifices in vitamin A deficiency was interestingly analyzed in a clinical paper (30). The lesions of a pathologically well defined disease, called pityriasis rubra pilaris, consisting of follicular hyperkeratosis and perifollicular inflammation, responded extremely well to the daily administration of 100,000 to 200,000 units of vitamin A, whereas the associated keratosis pilaris in the same patients (follicular hyperkeratosis without inflammatory signs) did not respond to vitamin A but responded very well to carotene intake.

A severe disturbance in a three-year old boy with hepatomegaly, splenomegaly, hypoplastic anemia, leucopenia, increased vitamin A and total lipid content of the blood serum, advanced skeletal development, coarse fingers and sparse coarse hair was traced by Joseph (31) to an A-hypervitaminosis. The boy received about 240,000 units of vitamin A daily since he was three months



old. Most signs cleared promptly on cessation of vitamin A administration.

*Magnesium.*—Much attention has been paid to cutaneous manifestations due to magnesium deficiency because it was claimed that in neurodermatitis the magnesium content of the skin is low, and the contention was that this abnormality may have something to do with the pathogenesis of the disease. Sullivan & Evans (32, 33) observed intense erythema, diffusely or in plaques, and extended edema in rats on the fourth to eighth day of a magnesium deficient diet. No similarity whatsoever was found to neurodermatitis, macroscopically or microscopically. The signs rather resembled those of pyridoxine deficiency, but the two conditions could be well differentiated and the magnesium deficiency remained uninfluenced by addition of vitamin B. Addition of vitamin E did not influence the signs of magnesium deficiency either.

Disturbances of hair growth in consequence of nutritional deficiencies as reported in the foregoing paragraphs seem to be secondary to serious disorders in epithelial cell life and in circulation. However, a remarkable observation of isolated disturbance of hair growth was made by Nielson & Black (34). When sulfasuxidine was fed to rats, a biotin and folic acid deficiency developed. When folic acid and biotin were added to the diet, the sulfasuxidine rats grew well but developed symmetrical patchy alopecia. This alopecia could be prevented by supplementing the diet with inositol. That hair loss in nutritional deficiencies may be subject to endocrine influences was assumed by Elvehjem *et al.* (14). Mulligan (35) observed patchy hair loss and thinning of the hair diffusely in male dogs when fed 5 mg. of diethylstilbestrol daily over a period of several months. Such dosage, of course, is extraordinarily high, and the observation has toxicological rather than physiological significance.

The pattern of hair growth in rats (36) and in rabbits (37) was found to take place in a series of waves symmetrically disposed about a long axis. The cutaneous capillaries showed greatest density along the advancing edge of the growing hair. It was obvious that the hair growth varied with a rhythmic alteration in the distribution of blood to the follicles. Observation of the pattern was greatly facilitated by injection of an alloxazine derivative which stained the hair orange yellow. It reached the hair through the active capillaries of the growth zone.

## PIGMENTATION

Newer publications (38, 39) clearly indicate that the mechanism of nutritional achromotrichia is not well understood as yet. Graying of hair, elicited in pups by purified diets with synthetic B-factor supplements, could not be cured by addition of inositol, *p*-aminobenzoic acid, biotin, calcium pantothenate, or cysteine, whereas the hair color could be completely restored by addition of liver or whole dried yeast to the diet (38). It was shown (39) that avitaminotic graying may become irreversible (possibly due to permanent damage to melanoblasts) when the deficient diet was given over a sufficiently long period of time. The graying of male mice was counteracted to a certain extent by administration of theelin, but such effect of contrary sex hormone administration was not observed in females (39). In amplifying earlier work, Spoor & Ralli (40) reported that the adrenal cortex may be involved in achromotrichia due to B deficiency because adrenalectomy reverses the achromotrichia. More than that, the authors found that in adrenalectomized animals the amount of extractable melanin of the skin was increased above normal, in spite of deficient diet. Dehydration, produced by water deprivation or by hypertonic salt administration, caused similar changes as did a filtrate-factor deficient diet. The conclusion was that both the adrenal cortex and sodium chloride are involved in the metabolism of melanin.

*In vitro* experiments seem to substantiate the role of sodium chloride. Lea (41) demonstrated that in the tyrosine-tyrosinase system the inhibitory action of ascorbic acid on tyrosine oxidation is weakened when the sodium chloride concentration of the system is lowered from 0.9 to 0.5 per cent. Lea believes that the decreased sodium chloride content of tissues in Addison's disease leads to a more rapid oxidation of ascorbic acid which allows an increased oxidation of melanogens to melanin in adrenal insufficiency. The reviewers have noted an increasing number of data in favor of the theory that the skin of the white human race is nonpigmented because of the presence of anti-oxidant inhibitory compounds, and that hyperpigmentation, post inflammatory as well as endocrine, is due to the destruction or inactivation of the inhibitory agents. An unidentified "inhibitory factor" of pigment formation in mammalian skin was discovered by geneticists (42). In yet unpublished experiments in our laboratory it was found that this factor is

located in the epidermis of human skin, i.e., in the layer where melanin is formed. To the well-known *in vitro* inhibitors of tyrosine oxidation (glutathione, cysteine, ascorbic acid, *p*-aminobenzoic acid, and sulfonamides) two more compounds, thiouracil and thio-carbamide, were added by Paschkis *et al.* (43). In the tyrosine-tyrosinase system thiouracil proved to be as potent an inhibitor as ascorbic acid. The observed inhibition by the sulfur compounds could be overcome by copper and by iodoacetic acid. The authors considered both possibilities of the action mechanism: anti-enzymatic action and interference with the oxygenation of tyrosine. It seems to the reviewers that a competitive demand for oxygen is the most probable mechanism because the same inhibitions are observed in nonenzymatic oxidation systems (1).

Concerning the finer mechanism of inhibition Robinson & Nelson (44), working with tyrosinase and potato tubers containing *L*-tyrosine, came to the conclusion that in the presence of reducing agents, such as ascorbic acid, only a trace of tyrosine can be oxidized by tyrosinase. The first oxidation product, 3,4-dihydroxyphenylalanine, acts as a competitive inhibitor in the oxidation of tyrosine. As soon as dihydroxyphenylalanine is oxidized to the quinone, the latter is reduced back to the dihydroxy compound by ascorbic acid. Essentially, these results confirm earlier work of Raper (45).

Using substrates other than tyrosine for oxidation by tyrosinase, Randall & Hitchings (46) found that among phenethylamine derivatives the 3,4-dihydroxy compound was most rapidly oxidized. The hydroxylation of the benzene ring in the positions 3 and 4 (relative to the side chain) is no doubt of great significance for melanin formation.

Sharlit (47) continued his studies on the Meirowsky phenomenon, i.e., the increase of pigmentation in excised or cadaver human skin when incubated at high temperatures or on exposure to ultraviolet light. He supplied definite proof that this phenomenon can be produced in complete absence of atmospheric oxygen and thus disproved the theory that the phenomenon is based on darkening of preformed pale melanin granules by oxidation in the air. He found that the phenomenon is enhanced by protoplasmatic poisons such as cyanides and fluorides, and considers the possibility that inactivation of the cytochrome system by chemical or physical means may result in an increased amount of active oxygen avail-

able for the pigmentary system. Sharlit feels, however, that the data on the Meirowski phenomenon have not disproved Bloch's theory on enzymatic oxidation of "dopa."

Several studies have been devoted to the local pigmentogenic action of hormones when applied topically. By applying testosterone propionate locally to the base of the bill of female and castrated male sparrows, Pfeiffer *et al.* (48) produced a line of black pigment at the zone of application. A total dose of 1.0  $\mu\text{g.}$  of the hormone was sufficient to produce this effect, when this total was distributed in equal amounts over a period of four, eight, or sixteen days. That there must be a direct local reaction between hormone and melanoblasts, without interference of circulating blood or nervous system (1), is evident from the observation that, if the hormone is given systemically, doses eighty times larger are needed in order to obtain the same effect. Androsterone had a similar effect to that of testosterone, but progesterone and desoxycorticosterone were ineffective. Estradiol benzoate did not counteract the pigmentogenic effect of male sex hormones. In the golden hamster the pigmentation of the dorsolateral subcostal region is a male sex character. Systemic administration of male sex hormone effected hyperpigmentation of this spot in males, castrate males, and females (49). Administration of estradiol benzoate or castration brought about depigmentation in males. No similar effect was obtained from desoxycorticosterone, progesterone, or estrogen.

Whereas the melanoblasts in the sparrow bill and in the masculine pigment spot of the golden hamster seem to respond specifically only to male sex hormone, those of the scrotal skin in mammals respond to both male (50) and female (51) sex hormone administration. Wells (50) produced scrotal pigmentation in ground squirrels by topical application of a total of 1.25  $\mu\text{g.}$  of testosterone propionate in alcoholic solution distributed over ten days. Davis *et al.* (51) obtained scrotal pigmentation in young castrated male guinea pigs by intramuscular injection of 25  $\mu\text{g.}$  of diethylstilbestrol daily for two weeks. The same authors demonstrated local action of stilbestrol by unilateral application of diethylstilbestrol to one nipple which resulted in unilateral pigmentation. They also have shown that the pigmentogenic effect of estrogenic substances is counteracted by the simultaneous administration of chorionic gonadotropic hormone. The authors believe that some similar inhibitory effect of pituitary hormones must be the cause for the

failure of stilbestrol to produce pigmentation in menopausal women, as the same doses of stilbestrol elicit deep brown or black pigmentation in cases of primary amenorrhea in young girls.

Changes in the plumage, particularly of its pigmentation, in capons and cockerels after administration of thiouracil were observed by Domm & Blivaiss (52). Replacement of black colors by red ones was reminiscent of changes following thyroidectomy. These observations may have interesting relations to the *in vitro* experiments cited above (43).

It has been known that the contractile melanophore cells of amphibians and fishes have a double antagonistic autonomic innervation, sympathetic impulses causing contraction, parasympathetic impulses causing expansion of cells, and the impulses resulting in lighter or darker skin colors respectively. More recent research indicates that the contracting fibers are adrenergic and the dilating fibers cholinergic. Parker *et al.* (53), analyzing the dark dorsal and the pale ventral skin of the catfish, *Ameiurus*, found from 0.02 to 0.08  $\mu\text{g.}$  of acetylcholine per gm. of moist skin in the dark portions, whereas the pale portion yielded only from 0.005 to 0.04  $\mu\text{g.}$

The melanophores of scales in some fishes show a rhythmic flow of pigment granules back and forth in the protoplasmatic processes of the cells. Marsland (54) examined the action of hydrostatic pressure on such pulsations in *Fundulus heteroclytus* and found that with increasing pressure the amplitude of pulsations becomes reduced and finally the movement ceases. The effect of pressure is independent of the nerve supply. Marsland (54) believes that the contraction of the cells depends upon their ability to undergo gelation whereas expansion involves sol formation.

The isolation of an iron pigment from human red hair, discussed in a previous review (1), was described in detail by Flesch & Rothman (55). A valuable comprehensive and exhaustive review on pigmentation of human skin, including color changes due to deposition of metabolites, with 399 references, was published by Jeghers (56).

#### KERATINIZATION PROCESS

One of the most important aspects of the problem of keratinization is the change in amino acid composition which the cell proteins undergo when keratinizing. Beveridge & Lucas (57) endeav-

ored to determine the most suitable reagents for and the best order of quantitative separation of the amino acids in hair hydrolysate. Arginine was separated in the form of the flavianate. Human hair yielded the following amounts of basic and dicarboxylic amino acids in percentages of total keratin: arginine 8.86, histidine 0.63 lysine 2.40, glutamic acid 10.6, and aspartic acid 3.5. The latter had never been reported previously as a constituent of keratin. An amino acid, tentatively identified as  $\beta$ -hydroxyglutamic acid, was present in 1 per cent concentration. In a fraction of the copper mercaptide precipitate of human hair hydrolysate methionine was found in the amount of 1 per cent (57). From wool 0.5 per cent methionine was isolated (58). A maximum yield of 4.3 per cent proline was obtained from human hair (57) by application of Town's copper salt method (59). Cystine and cysteine estimations in keratins of different origin were made by several authors (60, 61)

In continuation of earlier studies on -S-S- linkages in keratin Stoves (62, 63) demonstrated that these linkages are protected against oxidizing agents if the keratin is previously boiled with dilute formaldehyde solution at pH 6 (62). Protection against reducing agents could be accomplished by treatment with benzoquinone solution (63). Mitzell & Harris (64), dealing with the alkali cleavage of keratin in wool, favor the assumption that this cleavage primarily does not affect the -S-S- bond, but is connected with the rupture of a -CS- bond and with the formation of a dehydroalanine and a  $-\text{CH}_2\text{-S-SH}$  residue. According to the theory, these residues recombine after the latter has lost a sulfur atom and lanthionine, which the authors recovered in considerable amounts, is formed. Jones & Mecham (61) succeeded in dispersing keratin from feathers at a neutral pH and at as low a temperature as 40°C. with a minimum of hydrolytic action by employing neutral reducing agents and protein denaturants. The dispersion involved splitting of -S-S- bonds and of secondary linkages.

When keratin is ground, water-soluble proteins are formed. Previously this was explained by mechanical action which makes the soluble material accessible to the solvent. Cohen (65) showed, however, that grinding causes a wholesale disintegration of the keratin molecules, not confined to a cleavage of -S-S- bonds and salt linkages, but also breaking other bonds so that fragments of small molecular size result. A high degree of decomposition was

indicated by the fact that in the ground keratin no tryptophane was found.

De Castro & de Almeida (66) demonstrated that fluorescence of horny appendages and hyperkeratotic cutaneous lesions in filtered ultraviolet light is due to their keratin, and not to their lipid content.

An interesting influence of male sex hormones on localized keratinization, reminiscent of estrogenic cornification in the vagina, was reported by Burrows (67). In mice the foreskin detaches from the glans penis after birth. By castration this detachment can be prevented. However, when testosterone propionate is given to castrated males, there will be a separation of the prepuce from the glans. The separation is due to keratinization of the epithelium as shown by histological examination.

#### LIPID SECRETION

It has been known from clinical experience that sex hormones exert a profound growth stimulus on sebaceous glands. Their pubertal development was experimentally reproduced by Rony & Zakon (68), who administered testosterone propionate to boys aged eight to nine years, and examined biopsy specimens histologically before and after treatment. A considerable increase in number and size of sebaceous glands was found in all subjects after treatment. One half of the subjects also showed increase in number and size of hair follicles and sweat glands. However, there was no influence on hair growth.

Doupe & Sharp (69) were unable to find any evidence that the activity of sebaceous glands is directly under the control of the nervous system. In a subject with sympathectomy and in one with a lesion of the brachial plexus they were unable to demonstrate any change in sebaceous gland secretion in consequence of denervation. On the other hand, Rothman (70) pointed out that the pathologically increased flow of sebum in encephalitis is best explained by the assumption of an inhibitory center in the mid-brain, and quoted experimental data in favor of this assumption. Meltzer & Deme (71) made the remarkable observation that pilocarpine greatly enhances the first phase of sebum formation, i.e., a histochemically demonstrable formation of a fatty "pre-sub-



stance." Also by using histochemical methods, Meltzer (72) tried, but was unable to confirm, the old contention that eccrine sweat glands secrete any fatty substances.

#### SWEAT SECRETION

During the war, in tropical and subtropical regions with troops performing hard work in hot and moist climates, the physiology and pathology of sweat secretion, particularly the problem of acclimatization, became once more a vitally important topic.

Conn & Johnston (73) examined acclimatized men performing heavy work at 85°F. and 85 per cent humidity, and producing 4 to 9 l. of sweat in twenty-four hours. These men remained in sodium chloride balance and retained their physical fitness on an intake of as low as 5 gm. of sodium chloride per day. This acclimatized behavior was due to a sharp fall of the urinary output of sodium chloride and to the ability of the sweat glands to produce a fluid containing lower concentrations of salt when the salt supply was diminished. Johnson *et al.* (74) found that acclimatization primarily involves a progressive decrease of skin and body temperature, followed by a decrease of chloride excretion. Their experiments have shown that if rectal and skin temperatures remain the same, the chloride content of the sweat will not be different before and after acclimatization.)

Borden *et al.* (75) studied "heat disease" at a military post with high external temperature, high humidity and low wind velocity, and with a high casualty rate among the troops from the effects of heat. While vaporization of water from the skin surface depends mainly on the relative humidity of the air, the authors found that the wet bulb temperature is a more sensitive indicator of the probable incidence of heat disease than the relative humidity *per se*. A wet bulb temperature of 78 to 79°F. with a wind velocity below 10 miles per hour was considered to be the danger point for any physical activity, if the dry bulb temperature was 88°F. or over.

The use of 0.1 per cent salinized water for drinking purposes had been found to be the most practical means against excessive water and salt loss. Ladell (76) has demonstrated that, when chloride retention is created in man by injections of desoxycorticosterone, the salt loss with sweat is diminished about 30 per cent. The chloride concentration fell from 0.65 to 0.45 per cent under the influence of desoxycorticosterone injections.

A remarkable sudden breakdown of thermoregulation in mammals when subjected to drastic dehydration was described by Adolph (77). Seven different species of mammals were induced to lose water by evaporation during exposures to dry hot atmospheres but under conditions which permitted keeping of the rectal temperature below 40°C. After water equal to 10 per cent of body weight was lost, the body temperature climbed explosively and death ensued. If an animal was removed from the heat at the critical threshold, it might recover its water content but suddenly died without hyperthermia two to twenty-six hours later. In man, a sudden failure of the sweat mechanism was studied by Wolkin *et al.* (78) on soldiers in the American desert area. This "thermogenic anhidrosis" was preceded by a short period of hyperhidrosis and followed by recovery in a few days when the soldier was removed to cool quarters. During the anhidrotic period no sweating could be produced by administration of pilocarpine, mecholyl, hot tea, or aspirin. Salt intake did not prevent the syndrome. The authors were unable to decide whether this failure of sweating was of central or peripheral origin. Physiological heat regulation is also greatly disturbed when men work hard in cold weather in standard Arctic uniforms (79); sweat is recondensed in the clothing and does not achieve skin cooling. During rest periods some of the condensed sweat is evaporated, thus increasing the loss of heat just when heat conservation is needed. When men working hard at 0°F. wore light clothing, their sweating was reduced from 350-400 to 50 gm. per hour. The authors concluded that men could and should "underdress" while working at low temperatures.

*Electrical resistance of the skin.*—This is essentially an indicator of sweat gland function, and therefore also of the activity of the sympathetic nervous system. Ryan & Ranseen (80), measuring palmar skin resistance in periodically repeated exercise, found a statistically significant relationship between electrical skin resistance and physical fitness. Sleeplessness caused unusually high resistance and retardation of its initial fall during work. Heavy muscular work without an adequate period for recovery also raised the level of palmar skin resistance. Richter *et al.* (81) mapped out sharply defined areas of low electrical resistance on the palms extending to the side surfaces of hands, and on the soles extending to the sides of the feet in form of small bands and to the toes. There was a relation between these areas and the number of sweat glands, and the reviewers noted a striking similarity of these areas

with the localization of the eruption called "dyshidrosis" which might or might not be connected with sudomotor nerve impulses. The described areas of low resistance become constricted at low temperatures and during sleep. They enlarge at high temperatures, during exercise, and in excitement (81) and also in response to painful stimuli (82), obviously because of sympathetic discharges which follow pain sensation. Such discharges also accompany motion sickness (83). It was pointed out (84) that measurement of electrical skin resistance can well be utilized in neurological diagnostic work as a reliable indicator for impairment of sympathetic pathways.

As far as regional distribution of sweating is concerned Weiner (85) found that 50 per cent of the total sweat comes from the trunk, 25 per cent from lower limbs, and 25 per cent from head and upper limbs. The sweat rate per surface unit is greater on the trunk than elsewhere. As acclimatization proceeds, the rate of sweating increases during several days. In agreement with Kuno, Weiner (85) finds that the sweat glands of palms and soles are more sensitive to emotional and other mental impulses than to thermal stimuli. In this connection it might be mentioned that patients with atopic dermatitis, supposedly emotionally unstable individuals, and often those suffering from dyshidrosis (see above), excrete more palmar sweat with a lower chloride concentration than normal persons (86).

When sweat was collected by means of a capillary pipet from one finger in a heated collection chamber so that evaporation could be completely avoided, the sodium chloride concentration was found to be surprisingly high, from 650 to 1,450 mg. per 100 cc. (86). No correlation was found between the levels of sodium chloride in blood, urine, and sweat, nor between pH of urine and sweat. The pH of sweat varied in these experiments between 5.2 and 6.75.

Earlier data on high ascorbic acid values in sweat (1) have been corrected (87). No ascorbic acid is lost with the sweat, not even immediately after administration of ascorbic acid. However, the small amounts of dehydroascorbic acid present in sweat can be slightly raised by administration of ascorbic acid (87). Ascorbic acid added to sweat at body temperature is rapidly destroyed (88). This is not an enzymatic action because decomposition takes place even more rapidly by boiled sweat. No thiamine, diphosphothiamine, and no riboflavin was found in the sweat (88), although these vitamins were not destroyed when added to the perspire. Nicotinic acid was found in an average concentration of 0.05 mg. per

100 cc. sweat (88). Pyridoxine secretion with the sweat in adult males who were given 8 mg. pyridoxine per day was found to be too small to be of any significance in respect to the increased need of pyridoxine in hot climates (89).

#### INSENSIBLE PERSPIRATION

Burch & Winsor (90) measured the insensible loss in weight of man in a subtropical climate and confirmed earlier data indicating that water loss through skin and through lungs is approximately equal. Sodeman & Burch (91) found great individual and regional variations in insensible perspiration. (At 75°F. and 50 per cent humidity it was greatest on hands, feet, and head, at 105°F. on finger tips, axillae, and forehead.)

(It has often been assumed that transepidermal insensible perspiration is mainly a physical process due to diffusion of water from an inside with high water content to the outside, the water content of which is relatively low. Thus it is not surprising that the rate of insensible perspiration from skin which had been separated from the body was found to be the same as in living subjects (92). Also, it could be expected that the "insensible perspiration" would be greatly increased in a denuded area after removing the top of a cantharis blister when this top included the granular layer in addition to the horny layer (92). The granular layer was recognized as a barrier for water and electrolytes a long time ago; whereas there is no reason to assume that it is the horny layer, a loose meshwork of horny lamellae, which withholds the water (1). Still, Winsor & Burch (92) arrived at the conclusion that the stratum corneum was the main layer responsible for the inhibition of water-diffusion through human skin (92) and for preventing loss of water in edema (93).

Felsher & Rothman's work (94) led to an entirely different concept. They measured the insensible perspiration of humans in skin areas with pathologically increased production of keratin. They found three to ten fold normal values in lesions of psoriasis and exfoliative dermatitis, conditions in which there is a true hyperproduction of keratin. In ichthyosis vulgaris, where hyperkeratosis is due to incomplete separation of horny lamellae but not to increased and accelerated formation of horny material, the insensible perspiration values were in the normal range. It was shown that arterial hyperemia without increase of keratin formation does not essentially alter the insensible perspiration but that it is con-

siderably elevated during postinflammatory scaling. The conclusion was drawn that the physiologically continuous keratinization process, because it is connected with an enormous dehydration of keratinizing epithelial cells, contributes one part of the insensible perspiration. Whenever keratinization is accelerated the insensible perspiration increases. However, the formidable perspiration values found in exfoliative dermatitis and in some cases of psoriasis could not be accounted for by accelerated keratinization alone. It was assumed that in these conditions discontinuity of the granular layer increases the cutaneous permeability for water and thus contributes to the increase of insensible perspiration.

#### VASCULAR REACTIONS

It has been known from direct capillary observation that with the menstrual cycle there is a cyclic variation in the tonicity of cutaneous capillaries. Tentatively some of the circulatory disturbances of the skin with capillary ectasies and with stasis, such as rosacea, were attributed to deficiency in estrogens. In a clinical report McGrath & Herrmann (95) claim good therapeutic effect of estrogen administration in vasospastic conditions, such as Raynaud's disease and Buerger's disease. The authors believe that the estrogens act as dilators by releasing acetylcholine locally. However, in pregnancy, in which the amount of circulating estrogens is increased, no essential change of cutaneous capillary circulation could be demonstrated by Roberts *et al.* (96). The only consistent change they found in the skin of pregnant women was an increase of lymphatic flow when this was measured by the spread of intradermally injected dyes. Chiti [quoted by Lutz (3)] finds that in healthy women, premenstrually and during the first day of menstruation, the capillary resistance decreases. It might be in connection with the estrogenic cycle of cutaneous blood flow that during estrum an increased mitotic activity is found in the epidermis of mice (97). The greatest number of mitoses was counted during estrum and a minimum number on the first day of the diestrus. In the preestrus the number of mitoses varied directly with the number of maturing follicles.

In extended studies on denervated limbs Doupe *et al.* (98), using the skin temperature as an index of peripheral circulation, endeavored to clarify the problem of why sympathectomized limbs stay warm while denervated digits become cold. They came

to the conclusion that the tendency to coldness in denervated digits is due to the hypersensitiveness to the local vasoconstricting action of cold, and that in turn this hypersensitiveness of contractile elements is caused by the degeneration of sympathetic fibers. They did not find any essential difference in peripherally denervated and in ganglionectomized digits; if differences occur, they may be ascribed to the persistence of some postganglionic fibers after ganglionectomy. There is one consistent difference, however, between vessels of denervated and of preganglionectomized digits: to intravenous injection of epinephrine there is in the first case a lowered threshold and prolonged response, and in the second case only a lowered threshold. The mechanism of cold sensitivity is thoroughly analyzed by Doupe, and much thought is given to the possibility that the reduction in cutaneous blood flow at reduced temperatures is secondary to a local reduction of metabolites and corresponding changes in tissue pH. Otherwise, Doupe finds, the blood flow to denervated digits is adequate to the needs of the tissues, and the term "trophic" for ulcers developing in denervated areas is unwarranted. These ulcers follow traumatization and heal slowly because of impaired lymph drainage (with development of edema) and not because of lack of nourishment due to denervation.

The adjustment to high and low external temperatures of blood flow through normal skin was studied by Spealman (99). He found that the flow passes through a minimum as the temperature of the skin is gradually lowered. This conclusion was verified by plethysmographic measurements. Lewis (100) succeeded in supercooling the human skin to  $-25^{\circ}\text{C}$ . without freezing it. Such cooling was regularly followed by the urticarial triple response.

By measuring skin temperature Roth *et al.* (101) demonstrated that smoking has a considerable vasoconstrictor effect on cutaneous vessels. By means of the capillary microscope Pelzer & Redisch (102) observed the effects of some sympatho- and parasympathomimetic drugs on the cutaneous capillaries in anesthetized rhesus monkeys. The drugs when given intravenously showed the following effects: pilocarpine—narrowing of the venous limbs; acetylbetamethylcholine—widening of both limbs; atropine—slight widening but marked vasodilation if given after pilocarpine; epinephrine and drugs of the ergot group—narrowing; and nicotinic acid and nicotamic acid—widening. Whereas previous studies

and clinical observations in man indicated the occurrence of vasomotor disturbances of the extremities in vitamin B deficiencies, such effects could not be demonstrated by Roth *et al.* (103) in severe thiamine deficiency, in isolated restriction of riboflavin, or in restriction of the B complex induced experimentally in healthy women.

The dilatation of papillary and subpapillary cutaneous capillaries under the influence of therapeutic x-ray doses was precisely measured by Pendergrass *et al.* (104). When the same number of roentgens was administered, more persistent changes were recorded with soft x-rays (50 kv. peak voltage) than with more penetrating radiation (200 kv. peak voltage). Bereston (105) found increased sunburn reactions in patients inflicted with hemiplegia or paraplegia. This was in contrast to allergic reactions and to the flare reaction to histamine which were diminished throughout in paraplegics. Capillary reactions to ultraviolet radiation are greatly dependent on the opacity of the stratum corneum because this layer acts as a filter for the "erythema rays" of the ultraviolet spectrum (106). The absorption spectrum of *p*-aminobenzoic acid completely embraces the sunburn action spectrum, and therefore *p*-aminobenzoic acid is a powerful sun protectant if applied to the skin in ointments (107). When irradiated *p*-aminobenzoic acid is injected intradermally an inflammatory reaction results. Rothman & Rubin (107) consider the possibility that the photochemical change of *p*-aminobenzoic acid, if it is present in the skin, may contribute to the sunburn reaction in man. This would explain the peculiar shape of the sunburn action-spectrum.

#### CAPILLARY PERMEABILITY

Previously it has been generally assumed that when salts of acetylcholine or its derivatives are injected intradermally or introduced electrophoretically into the skin of humans, urticarial wheals are not produced by any concentration, unless there is a specific hypersensitiveness to acetylcholine as it is found in cases of heat and emotional urticaria (1). Lewis (108) states that such generalization is not permissible because he finds that a great many normal women do respond with whealing to electrophoretic introduction of acetylcholine. Still, Lewis believes that the evidence which is left in favor of the theory that cholinergic fibers are involved in his case of heat urticaria (1) is strong enough and the



theory does not need to be dropped. However, on the basis of a literary review Doupe (98) concludes that peripheral release of acetylcholine by posterior root fibers, an essential link in Lewis' theory, is unproved. Doupe also brings strong arguments against the assumption of release of H substance by skin cells under the influence of nervous stimulation.

Increased capillary permeability for proteins under the influence of intra-arterially injected histamine was demonstrated by Stead & Warren (109). The physiological content of histamine in the skin was dealt with by Alexander (110) who found that more than 60 per cent of the total histamine content of the body in mice is in the skin (average values, 300 $\mu$ g. total; 200 $\mu$ g. in skin). Marshall (111) working on rats demonstrated a substantial increase of the average histamine content of the skin following adrenalectomy, a remarkable fact in view of the often claimed increased susceptibility to anaphylactic shock of adrenalectomized animals.

When acid and basic anilin dyes were injected intravenously to guinea pigs, it was observed that cerebral capillaries were permeable to basic dyes only, and cutaneous capillaries were permeated only by acid dyes (112).

Lange (113) used a "dermofluorometer" (114) to measure the fluorescence content of the skin after its intravenous injection. In this way a greatly increased capillary permeability was found in myxedema. The values returned to normal after thyroid medication.

Bourne (115) supplied further evidence for the existence of vitamin P by demonstrating greatly increased fragility of the cutaneous capillaries in guinea pigs which were given a scorbutogenic diet with addition of vitamin C. Citrin proved to be curative.

#### PERCUTANEOUS ABSORPTION

Strakosch & Clark (116, 117), examining the penetration of sulfonamides into intact human skin, found that the type of the ointment base (oil-in-water and water-in-oil emulsions) is entirely irrelevant for the rate of absorption, and that addition of solubilizers and wetting agents to the ointment do not increase the penetration either. By prolonging the time period of application the amount of absorbed material was correspondingly increased, but no increased absorption could be forced by increasing the concentration of the sulfonamide compound in the ointment.

There was a greatly increased absorption through broken skin, and there the absorption was greater from wet packs than from ointments, possibly because of better wetting of denuded moist areas by aqueous solutions than by grease. Miescher & Burckhardt (118) confirmed earlier data concerning increased percutaneous absorption in guinea pigs after treatment of the skin with acetylcholine, with histamine, and with testicular extracts. Absorption by human skin was not influenced by such procedures. Beutner *et al.* (119), dealing with the absorption of methylsalicylate, found easy penetration and no difference in the rate of absorption from greasy and nongreasy ointment bases. Walzer & Sack (120), working on men and monkeys sensitized to cottonseed, demonstrated that petrolatum and anhydrous wool fat are equally efficient vehicles for percutaneous introduction of the cottonseed allergen. Alkalinization of the petrolatum ointment hastened absorption.

In careful histological studies MacKee *et al.* (121) studied the penetration of heavy metal compounds, sulfonamides, and dyes through the skin of guinea pigs and men. These compounds were incorporated as "tracers" in different types of vehicles. Contrary to others (117), the authors found better penetration of aqueous solutions when wetting agents were added. Best penetration was obtained by use of vehicles combining water, propylene glycol, wetting agents, "coupling agents" (antipyrine), and solubilizers. With these vehicles staining of the follicles, epidermis, and corium was achieved. However, in all cases a band free of color approximately corresponding to the stratum lucidum was observed. In their interpretation the authors outlined the main route of penetration as follows: horny layer→follicular pores→follicles→corium via both sebaceous glands and sidewalls of follicles→spread in corium downwards, to the side, and up into the epidermis. According to this scheme the epidermal barrier (1) is not broken through, neither from above nor from below.

As could be predicted, because of its lipid solubility, DDT (2,2-bis[*p*-chlorophenyl]-1,1,1-trichloroethane) was shown to penetrate the intact skin when applied in dimethylphthalate solution (122). It is of great practical significance that doses as low as 0.5 cc. of a 30 per cent solution per kg. per day were found to be toxic when applied to the skin of rabbits, guinea pigs, and rats for thirty days. Triorthocresyl phosphate which is found as an

adulterant in Jamaica Ginger and causes "ginger paralysis" was shown by Hodge & Sterner (123) to penetrate the skin of dogs and men with great ease. Cumulative doses in animal experiments led to paralysis. The data indicate that continued contact may be harmful to man. The tracing of the compound was accomplished by applying radioactive phosphorus. McNally & Fostvedt (124) demonstrated that mercuric cyanide is not absorbed from soaps by the skin of dogs. McClellan *et al.* (125) confirmed earlier data on the easy transportation of carbon dioxide through human skin from natural mineral water baths.

Miescher & Burckhardt (118) have disproved the claim that aniline dyes are absorbed through desquamative cutaneous lesions of man. They found it true that such lesions, when painted, decolorize earlier than normal skin, but showed that this happens because the dye is cast off with the horny material.

#### SENSORY PERCEPTIONS

Bishop (126, 127, 128), in his work on cutaneous pain sensation, contributed data to the physiology of itching. He isolated peripheral units of pain perception in human skin by means of elaborate local anesthetic procedures. From the high points of these units, with increasing quantity of stimulation, nonpainful prick, itching, and pain sensations could be obtained with a definite qualitative shift and with no merging of these different sensations. It seemed that with increased frequency of fiber response the sensation was switched to a different central recording system. Or, in other words, elicited from the same peripheral units, sensory impulses reach the brain and undergo qualitatively different interpretation within the modality of pricking pain, dependent only upon the intensity of the stimulus (127). Itching without accompanying prick sensation could be elicited by low intensity, high frequency stimulation of prick endings. It also was experienced as an after effect of slowly repeated stimuli, each of which caused an initial sharp prick. In experiments involving removal of the skin to various depths Bishop (128) found a one-to-one relation between hair follicle groups and pain spots. Histological work indicated that the extreme sensitivity of the central high point in a unit pain area might be correlated with its position directly over a pain twig, so that nerve endings of several fibers might be activated by a stimulus at one point. Contrary to

most previous reports on intraepithelial nerve endings, Bishop finds most nerve endings below the epidermis or just reaching the basal layer. He believes that this is because others have examined only regions with thick epidermis whereas his preparations are taken from thinly epithelized regions. However, lately, Marques (129) presented excellent gold-impregnated preparations with nerve elements reaching the stratum granulosum in a rather thin epidermis.

#### CHEMICAL CONSTITUENTS

A sound foundation for all future pathochemical research in dermatology has been laid by Eichelberger *et al.* (130, 131) by systematic chemical determinations of water, electrolytes, and nitrogen in the skin of dogs and humans. In their work on dogs (130) the authors have convincingly shown that all the deviations and contradictions in the results of earlier workers were due to the fact that they neglected the extremely variable fat content of the skin and calculated their data simply on the basis of either dry or wet skin. By working with fat-free skin and by preparing a homogenous skin powder by a special freezing method, Eichelberger *et al.* (130) found surprisingly constant water content and electrolyte concentrations in the skin of normal dogs. Potassium and magnesium concentrations were low in comparison with values in other tissues, indicating a small intracellular phase. Sodium and chloride values were high, indicating a large extracellular phase. In human skin the variations were greater than in canine skin. The water content varied between 69.0 and 74.0 per cent, the total nitrogen content between 38.6 and 52.3 gm. per kg. of fat-free skin. Separate estimation of collagen nitrogen revealed that collagen represents two-thirds of the solid matter of the skin. In spite of greater variations in man, the standard deviations were smaller than in any other previous work, and there was a remarkable similarity in the analytical results between human and dog skin, the only exception being markedly lower potassium values in human skin (Table I).

Attempts were made (131) to calculate the total connective tissue nitrogen and the connective tissue weight from the collagen nitrogen content on the assumption that the ratio of collagen nitrogen to total nitrogen is the same in all connective tissues as it is in tendon. This assumption is open to criticism. It is evident

from histological observation that the ratio of fibrillary to interfibrillary substance varies greatly among connective tissues of different organs and even within different layers of the same organ, e.g., the skin. However, the general conclusion of the authors that "the amount of the intracellular phase of the skin is small" is certainly valid.

In pregnant dogs (130) there was an increased water content (75.2 per cent), decreased nitrogen content, and normal electrolyte concentration in the skin, and essentially the same situation was found in dogs made hypertensive by the Goldblatt technique (74.7 per cent water). When hypertensive dogs were given isotonic salt infusions, there was a rise from 75 to 82 per cent water in the skin, a much higher increase than in any other tissue under similar conditions. This result confirms earlier data indicating that the skin is a reservoir capable of taking care of a considerable part of any excess fluid added to the body.

Haldi *et al.* (132, 133) continued their studies on the water and fat content of the skin of albino rats on various diets, and found on a high fat diet a substantial decrease in water and protein, and increase in fat as early as at the end of one week of dieting. In vitamin B deficiency (134) the water content was increased because of generally reduced food intake ("hunger edema").

The proteolytic enzyme, isolated from the skin of man and laboratory animals by Beloff & Peters (135), is active at a pH which is close to that of trypsin activity. It is relatively heat stable and seems to be liberated when the skin is burned. The authors believe that the enzyme possibly plays a role in blister formation. Thompson & Whittaker (136) studied the esterases of human skin and rat skin and succeeded in separating a true specific cholinesterase from the esterase which splits tributyrin.

#### TECHNIQUES

To elicit profuse sweating in man, Guttman (137) recommends parenteral injection of 3 to 5 mg. of furmethide (furfuryl trimethylammonium iodide). This drug proved to be superior to pilocarpine but in some cases caused slightly annoying side reactions. For visualization of sweat secretion Silverman & Powell (138) suggest the painting of a diluted alcoholic ferric chloride solution on the dry skin, allowing to dry, and applying to the skin a mimeograph paper which has been soaked in either tannic

acid solution or in a 5 per cent solution of potassium ferrocyanide. In presence of moisture tannic acid will cause a grey-blue or blue-black color; ferrocyanide will effect formation of prussian blue. Rose (139) favors the Guttman test (1937) in which the sodium salt of quinizarin-2-6-disulfonic acid is used. This is a reddish-grey powder, its color changing to deep purple in the presence of moisture.

Stowell & Cooper (140) combined histochemical reactions with photometric measurements so that relative amounts of stained particles could be estimated. In this way and by use of the histochemical Feulgen reaction it was shown that in hyperplastic epidermis the amount of thymonucleic acid per unit volume is less, and in carcinomatous epidermis more, than normal.

TABLE I  
ANALYSES OF HUMAN AND DOG SKIN\*

	H <sub>2</sub> O gm.	Cl mM	Na mM	K mM	Ca mM	Mg mM	Total N gm.	Collagen N gm.
Human skin								
(18 subjects)	254	28.3	32.9	5.83	0.95	0.75	16.1	11.9
$\sigma$	23	2.6	4.5	1.27	0.22	0.12	0.2	1.1
Dog skin								
(10 subjects)	243	29.7	33.1	7.71	1.03	1.04	16.0	11.3
$\sigma$	24	2.3	3.2	1.14	0.20	0.08	0.3	0.8

\* From Eisele & Eichelberger (131); values are expressed in units per 100 gm. of fat-free solid.

$\sigma$  Standard deviation.

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SECTION OF DERMATOLOGY, DEPARTMENT OF MEDICINE  
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## DIGESTIVE SYSTEM\*

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*Mouth and esophagus.*—From 1,552 electrometric tests made with the glass electrode at regular bihourly intervals for an entire year Eisenbrandt (1) found the mean pH of saliva of seven subjects to be  $6.64 \pm 0.006$ . The pH of saliva for the group varied markedly during the year and indicated seasonal fluctuations. The results on the subjects were significantly variable for each month and for the year, although each one tended to follow the general trend of the group. The pH of saliva of the group was lowest at 9 a.m., was always greater at 11 a.m., passed through the yearly average at 1 p.m., and was highest at 5 p.m. The pH of saliva for the group was significantly variable from month to month at each bihourly period. According to Brassfield (2), overventilation in dogs receiving a continuous injection of pilocarpine produced an increase in the pH of both blood and saliva. These changes were attributed primarily to decreased carbon dioxide tensions. The change in salivary pH was smaller than the pH change in the arterial blood. Administration of low oxygen in a mixture containing carbon dioxide approximating the tension of carbon dioxide in the arterial blood produced a greater decrease of pH in saliva than in arterial blood. Disturbances of cellular metabolism induced by the impairment of oxidations probably contributed to this decrease in salivary pH. Since an increased salivary flow accompanied the decreased salivary pH but preceded the decrease in blood pH, the increased secretion was attributed to an increased intracellular acidity. Inhalation of air containing more than 8 per cent carbon dioxide produced initially a greater pH decrease in blood than in saliva. After the initial decrease in saliva pH an increase was obtained and a further increase occurred on returning the animal to room air. Lower percentages of carbon dioxide only produced increases in salivary pH. Pratt & Eisenbrandt (3) devised a new method for determining the amylolytic activity of saliva. The variations obtained in six individuals studied by this method were statistically significant. Salivas tested with "Hydriion" paper by Turner &

\* This review covers the literature to July 1945.

Crane (4) showed considerable variation in pH, but there was no correlation between these pH readings and the amount of caries. However, the diastatic index of saliva was found to be inversely related to the amount of caries. According to Harrison & Opal (5), the lactobacilli found in the intestines are derived from the mouth and are continuously replenished by swallowing lactobacillus-contaminated saliva. No lactobacilli were found in stool specimens from five children whose teeth were caries-free. During this period lactobacilli were only occasionally recovered from the saliva of these subjects.

Grau (6) described a condition characterized by the folding back of the tip of the tongue of chicks. A deficiency of isoleucine, leucine, or phenylalanine caused this syndrome, whereas deficiencies of protein or of several other amino acids had no effect. Gradual healing occurred about a week after chicks were placed on an adequate diet. Alvarez (7) claimed that heartburn is largely due to regurgitation into a sensitized esophagus and partly to reverse waves of peristalsis coming up from the stomach. The roentgenographic appearance of the esophagus in normal infants studied by Bakwin, Galenson & Levine (8) showed the opaque material frequently distends the lower esophagus during a meal and for some time after a meal. Ordinarily, this is due to regurgitation from the stomach rather than to stasis or obstruction at the cardia. Lehmann (9) found that stimulation of the cervical vagus in the dog causes relaxation of the cardia, followed by contraction. The fibers producing contraction were found to be cholinergic, and they travel in the main trunks of the vagi. The inhibitory mechanism is within the wall of the lower esophagus. Interference with this inhibitory mechanism by bilateral vagotomy in the neck is followed by cardiospasm due to predominance of the sympathetic innervation which is motor in its effect on the cardia. Ergotamine causes relaxation of the cardia.

*Gastric secretion.*—Apparently gastric hydrochloric acid arises from an exchange of organic anions for chloride, according to Bull & Grey (10). This exchange takes place across a membrane impermeable to cations. The membrane probably is the intracellular canaliculus membrane in the parietal cell. The necessary concentration gradient of the organic anion across the intracellular canaliculus membrane is maintained by a rapid and rather complete

destruction of the organic anions by decarboxylation within the parietal cells. Very likely carbonic acid is directly concerned in the production of hydrochloric acid and pyruvic acid furnishes the exchangeable organic anion. Any specific inactivation of carbohydrate metabolism should lead to impaired gastric secretion. PinCUS *et al.* (11) observed that when acid is introduced into the small intestine of Pavlov pouch dogs it inhibits gastric secretion in response to a meal, provided an adequate degree of intestinal acidity is attained. Marked inhibition of secretion occurred if the pH of the intestinal contents were about 2.5 and almost complete depression when the pH was 2.0 or lower. This regulatory effect of intestinal acidity on gastric secretion was not present when the secretion was provoked by histamine. The required pH values are unusually low, and thus the authors look upon this mechanism as emergency in character.

Komarov and associates (12) essentially confirmed the report of Friedman that rats show some spontaneous gastric secretion even when anesthetized (urethane) deeply enough to eliminate the cephalic phase and when the small intestine and cecum are empty. Therefore, the gastric reaction is almost always acid. Histamine is not an effective gastric stimulus for the rat. Meat extract, liver extract, gastric and choline hydrochloric acid are effective stimuli. Smith, Wikoff & Southard (13) studied gastric secretion in normal subjects and found greater than standard variations in acidity. The amount of current required to produce gastric secretion by vagus stimulation shows a definite seasonal variation according to Fetter (14). Usually, this amount of current is the threshold current required to stop the heart. In a report of a four-year study of the mechanism of gastric mucus production and of methods of augmenting its formation, Hollander (15) described spontaneously secreted mucin as being less opaque, containing fewer cells, and being rather viscous in comparison with mucus from chemical stimulation. A determination of the rate of excretion and concentration as well as the intensity to which injected neutral red can be concentrated gives an excellent indication, according to Gillman (16), of the excretory function of the gastric mucosa. In normal subjects, the excretion of neutral red from day to day tends to remain constant even when acid secretion shows considerable variation. Acid secretion and dye excretion appear to be indicators

of two independent functions of gastric mucosa. However, he claimed that a comparison of neutral red and of acid secretion in normal and pathological stomachs indicated the neutral red tests might be a more reliable and sensitive tests of gastric function than the study of acid secretion.

Adrenalectomized rats in good general condition were found by Tuerkischer & Wertheimer (17) to show marked diminution of gastric secretion following stimulation with doryl. The gastric juice of such rats contained little or no free acid, only small amounts of total acid, was low in enzyme content and rich in mucin. Treatment with sodium chloride or desoxycorticosterone did not restore gastric secretory function which returned after adrenal extract administration.

Studying the excretion of sulfonamides in man, Schiff and associates (18, 19, 20) found the concentration ratio (concentration in blood concentration in gastric juice) varies directly with the blood level except with sulfapyridine and sulfathiazole. There is no relation between concentration ratio and the amount of free gastric juice. The mean concentration ratio is the same (0.45 or less) in normal subjects, patients with gastric or duodenal ulcer, or atrophic gastritis, or gastric carcinoma patients having free hydrochloric acid.

According to Beamer *et al.* (21), isotonic solutions of proteose ("Bactoprotone"), amino acids, or sodium chloride failed to elicit secretion of gastric juice in fasting dogs when administered into the intestine in the absence of bile. Bile alone was also without effect. However, a moderate amount of gastric secretion was obtained after a latent period of from one to two hours when "Bactoprotone" mixed with bile or hypertonic solutions of amino acids or sodium chloride were placed in the intestine.

Electroshock therapy in the studies of Fetter (22) had no effect on gastric acid secretion in patients whose acid was originally high, but in many patients with low acid during fasting, the electrotherapy elevated the gastric acidity. The gastric secretion induced by histamine in autotransplanted pouches and in vagally denervated pouches was found by Grossman *et al.* (23) to be inhibited by nausea and vomiting. Abdominal splanchnectomy and lumbar sympathectomy did not abolish this effect. In the process of extracting secretin from intestinal mucosa, a pepsigogue substance also has frequently been extracted. Babkin & Komarov (24) sep-



arated this substance and, on the other hand, demonstrated that crystalline secretin does not augment pepsin secretion.

Hollander (25) discussed the significance of measuring the gastric electrical potentials and the technical difficulties involved in these measurements. Rehm & Enelow (26) found that the oral ingestion of milk does not invariably significantly change the gastric potential. The passage of an electric current from serosa to mucosa of the secreting stomach was found by Rehm (27) to augment secretion. Passage of current in the reverse direction produced a more marked decrease in secretion and a depression of the potential. In the nonsecreting stomach, passage of current in either direction did not induce hydrochloric acid secretion.

Using the hemoglobin method of assay, pepsin was found by Bucker (28) in all urine samples from twenty-five female subjects. Storage of the urine for four days at 15°C. did not alter peptic activity. The pepsin content of any sample was well correlated with its specific gravity. The highest peptic potencies were found in urine specimens with low pH (4.5 to 5.0) and when the pH was 7.0 or more, little or no pepsin was found. In subjects having gastric pepsin, no relation was observed between gastric and urinary pepsin concentration. Individuals showed considerable daily fluctuations in the concentration of urinary pepsin, but the twenty-four hour output remained relatively constant.

According to Dawson (29) the argentaffin cells of the gastric mucosa of the rat are less numerous than had been reported. In the fundus, these cells usually are not intraepithelial but periglandular. In the pyloric glands, the cells are typically intraepithelial. In the animals studied (30) and in the human (31), argentaffin cells are more numerous in the fundic than in the pyloric portion of the stomach. In the fundic mucosa of the newborn rat, the cells appear at the time the gastric glands make their appearance and become more numerous as the rats grow older (32).

Srikantia, Hiriyanaiya & Kantiengan (33) prepared standard reference charts of gastric secretion showing the range of variation of maximal hydrochloric acid response to a Boas meal throughout the gastric cycle of young Mysorean men and women. No appreciable difference was observed in the gastric response of people on vegetarian or on mixed diets. In the nonsecreting stomach, according to Stavrakys (34), the intra-arterial administration of acetylcholine produces a secretion which differs in various parts

of the stomach but is alkaline or only slightly acid and contains pepsin. In the stomach under histamine influence, larger doses of acetylcholine also increase pepsin secretion but depress hydrochloric acid secretion. The drug also greatly augments gastric motility.

*Gastric motility.*—During motion sickness, Hemingway (35) confirmed the observation that gastric tone is depressed and the evacuation of a barium meal is delayed. Sturgeon, Henschel & Keys (36) were unable to detect any change in gastric evacuation rate or final emptying time between a control test meal and either a high carbohydrate, high fat, or high protein meal. However, Northrup & Van Liere (37) observed that addition of glucose delays evacuation of a meal to an extent roughly proportional to the glucose concentration.

Employing the pyloric diagraph Brody & Quigly (38) found the characteristic motility of the pyloric sphincter of the trained dog to consist of rhythmic contractions having a 10.4 to 14.1 sec. cycle. In the fed animal, the contractions tend to be more uniform, more continuous, and of greater magnitude than during fasting. In fasting rabbits Carmichael, Strickland & Driver (39) found the quantity of gastric contents had dropped 50 per cent after twenty-four hours, and after a few days, it consisted of only some hair and fluid. The contents of the small intestine likewise decreased but remained unchanged in viscosity, general appearance, and ratio of wet to dry contents.

Krueger (40) found that the temperature in the frog's stomach usually differs from the environmental temperature, being 1.7°C. below room temperature and from 3° above to 2.4° below the pool temperature.

Movements of the empty stomach of the monkey (*Macacus rhesus*), studied with the aid of a balloon introduced through a fistula, as observed by Alekseenko & Voronin (41), differed sharply from that previously described by Patterson. Instead of alternate periods of rest and activity, there was continuous activity, consisting of single contractions at two to three minute intervals. Occasionally, activity stopped for six to ten and even up to thirty minutes. With few exceptions, pain did not affect the motor activity of the stomach. Inhibition of movement for about ten minutes followed vomiting. Neither the smell nor the sight of food stopped contractions. Feeding was accompanied by either complete cessation of activity or by small, irregular, and continuous digestive

movements. Subcutaneous injection of pilocarpine completely inhibited contractions for fifty to sixty minutes while atropine inhibited for four to five hours. Small doses of acetylcholine had no effect; larger doses cause inhibition of movements lasting from eight to ten minutes, followed by small, frequent contractions lasting about ten minutes, and a frequent restoration of the normal activity.

*Peptic ulcer.*—The recent studies of the peptic ulcer problem involve many aspects of physiology. Rossett & Flexner (42) recorded gastric pH continuously in humans and demonstrated the buffering effect of a number of common antacids. While comparing the effectiveness of five antacids Clark, Adams & Romaro (43) found that sodium bicarbonate and calcium carbonate produce the greatest increases in hydrochloric acid secretion. Magnesium oxide had almost no secretory effect but none of the antacids tested decreased gastric secretion. According to Krantz, Kibler & Bell (44), aluminum dihydroxyamino-acetate neutralized gastric acid more promptly and 24 per cent more effectively than an equal amount of dried aluminum hydroxide gel. Grondahl & West (43, 45) were unable to demonstrate that the administration of aluminum hydroxide to a normal subject interfered with the utilization of dietary carbohydrates, fats, or proteins. Several groups of investigators (46, 47, 48) have failed to confirm the reported decrease in gastric secretion from the introduction of a jejunal pedicle graft in the gastric wall. The ingestion of magnesium trisilicate by humans was found by West & Pennoyer (49) to increase the serum magnesium level and the urinary and fecal pH. There was no interference with the utilization of dietary carbohydrates or fats, but protein absorption was decreased. Extensive tests on dogs, rats, and humans receiving moderate doses of an alkyl aryl sulfonate failed to disclose to Freeman *et al.* (50) any harmful effect. Large doses (3 to 4 gms. daily) produced death of dogs probably through inanition and dehydration.

Following a severe hemorrhage from a peptic ulcer, Levy (51) found that the serum proteins returned to normal twice as rapidly in patients receiving the Sippy diet supplemented with a 100 to 200 gm. mixture of amino acids as with the unmodified Sippy diet. Dogs on a protein deficient diet developed "peptic ulcers" which Li & Freeman (52) were unable to relate to any dietary abnormality other than protein restriction. The addition of rennin to 0.1 N

HCl applied under pressure to intestinal loops was found by Driver (53) to hasten the intestinal perforation. On the other hand, mineral oil protected the intestine. Rennin under pressure produced more necrosis than trypsin or erepsin while steapsin or amylopsin were inactive (54).

The rapidity with which pepsin hydrochloric acid solution applied under pressure to the intestine caused intestinal perforation increased as the pressure of the solution was augmented (55), but was counteracted by increasing the intra-abdominal pressure (56). Within limits, the concentration of pepsin in the solution did not alter the rate of mucosal digestion. Proximal intestinal loops generally were more resistant than distal loops and hydrochloric acid alone was much less destructive than pepsin-hydrochloric acid (57). Pancreatin in an alkaline solution or pepsin in an acid solution produce ulcers when applied to the dog intestine. In either case, the severity of the ulceration was considerably increased when the intestine was exposed to the preparation under pressure (58).

In anesthetized cats, exposure of gastric mucosa to ethyl alcohol or acetic acid was noted by Grant (59) to produce denudation of the epithelium. However, after a few hours healing occurred, which consisted first of the formation of an epithelium bridge, then a covering of low cylindrical cells which formed a new epithelium for the surface and for foveola. The foveola soon approached in depth and numbers the control mucosa. Dragstedt *et al.* (60, 61) obtained support for the belief that gastric hypersecretion in ulcer patients is neurogenic in origin by relieving this hypersecretion and also the ulcer pain and distress by supradiaphragmatic sectioning of the vagi. No disturbance in digestion developed. Vagotomy also relieves gastric hypertonicity and hypermotility in ulcer patients (62). It suppresses the secretory augmentation of a sham meal or insulin but not that of caffeine (63). Weinstein *et al.* (64), however, found that subtotal vagotomy has but little effect on gastric secretion or on the symptoms of ulcer.

The gastric acidity produced by histamine was found by Brown & Rivers (65) to be much higher in men suffering from ulcer than in women patients. Lannin (66) emphasized the use of physiological principles in the surgical control of peptic ulcer. The tendency to ulcer production is increased by obstruction of the splenic vein (67), by blunt impacts on the head (68), low calcium diets (69),

preparation of a gastroenterostomy with a long intestinal loop (70), war "trauma" (71, 72, 73), and by-fat emboli (74). Roth & Ivy (75 to 78) found that caffeine increases gastric secretion, acts synergistically with histamine to increase acid and pepsin secretion, produces vascular and cellular changes which augment the ulcer tendency, and produces experimental ulcers in the cat. Merendino *et al.* (79) confirmed much of this caffeine action in cats, guinea pigs, and dogs.

A favorable influence on human peptic ulcer has been obtained (80) with upper intestinal mucosal extracts (enterogastrone). This preparation also prevented ulcer formation in Mann-Williamson dogs and the protection had indications of an immunizing effect since it persisted for as long as three years beyond the period of administration.

The fasting contents of the duodenum in ten cases of duodenal ulcer were found by Comfort & Osterberg (81) to be similar to those in normal persons. The pattern of secretion of fluid, bicarbonate, amylase, trypsin, and lipase in cases of duodenal ulcer was similar to that seen in normal persons when purified secretin was used as a stimulant. Purified secretin evoked secretion of a greater volume of pancreatic juice and of a greater amount of amylase, trypsin, and lipase in cases of duodenal ulcer than in normal persons. The secretion of bicarbonate was approximately equal in the two groups. The data do not permit the conclusion that pancreatic secretion is deficient in cases of duodenal ulcer; on the contrary, pancreatic secretion (after stimulation with secretin) was equally as active in cases of duodenal ulcer as it was in the group of normal persons. Local application of equal parts of a sodium bicarbonate solution (8 per cent or saturated) and glycerine resulted, in the investigations of Cameron (82), in the disappearance of the lesion in eight out of sixteen uncomplicated rodent ulcers. Kirsner & Spitzer (83) present additional data concerning the action *in vitro* of sodium alkyl sulfate on the peptic activity of human gastric juice and of a standard pepsin solution. Sodium alkyl sulfate markedly inhibited *in vitro* the peptic activity of human gastric juice and of a standard pepsin solution. This inhibition apparently was an irreversible effect. Lactic acid in 0.2 ml. quantities exerted a slight protective action against the inhibiting effect of sodium alkyl sulfate. Similar amounts of formic, caprylic, and acetic acids were ineffective in this respect. Triacetin ethyl butyrate, ethyl caprylate,

ethyl laurate, ethyl myristate, and sodium taurocholate in 0.1 ml. quantities exerted a moderate protective action against the inhibiting effect of sodium alkyl sulfate.

According to Kernkamp (84) a gastric ulcer incidence of 2.4 per cent occurred in a total of 754 necropsies on swine. The ulcers were solitary in about 50 per cent of the cases, and multiple in the remainder. In most cases, the ulcers developed on the greater curvature of the stomach. Five of the cases were in pigs less than fourteen weeks of age and in each case a history of nutritional anemia was obtained. The lesion in every instance was discovered at necropsy but its presence was never suspected from subjective symptoms. The growth of transplanted lymphosarcoma cells, according to Williams (85), is inhibited by gastric mucin which augments the local "foreign body" and inflammatory processes sufficiently to destroy the neoplastic cells. The appearance of the stomach, hyperfunctioning under the influence of food, alcohol, histamine, or certain emotionally charged situations, resembles in certain respects described by Dailey (86) the stomach with hypertrophic gastritis.

*Intestinal absorption and secretion.*—Free & Leonards (87) ingested as much amino acid mixture or as much protein (blood and meat) as possible during eight hour periods. Apparently, the rate of intestinal absorption limits the amount of amino acids or of protein that can be ingested and the normal digestive tract handles large amounts of unhydrolyzed protein better than equivalent amounts of amino acids. Thiamine-deficient rats were found by Leonards & Free (88) to have a rate of galactose absorption which averaged 85 to 90 per cent of the controls. The rate of galactose metabolism was unmodified by suboptimal thiamine intake. Emerson & Obermeyer (89) found that thiamine-deficient rats excreted in their stools the same amount of thiamine as those receiving adequate thiamine but the fecal thiamine of the deficient rats was nonavailable when administered orally for curative purposes.

In anemia patients given radioactive iron, Hahn *et al.* (90) demonstrated that ferrous iron was much more readily absorbed and utilized than ferric iron. Hemorrhagic anemia in dogs also responded more readily to ferrous iron. Similar results were obtained by Moore and associates (91). By means of isotropic tracer studies on the movement of water and ions between the intestinal lumen and the blood, Visscher and associates (92) obtained results not pre-

dictable on the basis of osmosis and diffusion. There apparently is a forced flow of fluid across the intestinal epithelium in both directions simultaneously and the differences in the solute content of the water in the two streams determines the direction and magnitude of the net transport.

Cornatzer & Andrews (93) found that the amount of quinine sulfate, quinine dihydrochloride, and quinine alkaloid absorbed from the dog's intestine was not related linearly to time, since the absorption rate decreased greatly during the second and third half hour following drug administration. On an acid regime the excretion of quinine was about twice that on an alkaline regime (94). Sulfapyridine, sulfathiazole, and their sodium salts are absorbed in significant amounts from the stomach according to the report of Laughlin *et al.* (95), but with the exception of sulfadiazine, these compounds are absorbed still faster when not confined to the stomach.

MacLachlan & Thacker (96) found that corn oil absorption from the gut of rats was not affected by exposure to oxygen partial pressures as low as 80 mm. Hg. However, at pressures of 63 and 53 mm. absorption was significantly less. Cardini & Serantes (97) found that in white rats digesting olive oil, the fatty acid concentration of the intestinal mucosa increased to about twice the normal, but there was little change in phospholipids. The increase in the unsaturated fatty acid content of the mucosa preceded that of the saturated, but in the blood the latter increased first. According to the report of Mattil & Higgins (98) stearic acid is only slightly digestible, whether ingested as the simple triglyceride or as a mixed glyceride. The "solvent" action of oleic acid was somewhat greater in the mixed glycerides. Continuing the investigation of fat absorption Frazer *et al.* (99) found that triglyceride is finely dispersed to fat globules less than  $0.5\mu$  in diameter. The combination of bile salts and oleic acid monoglyceride is especially effective in producing spontaneous emulsification and good stability at all points of the intestinal pH range. Paraffine emulsified to average particle diameter of  $0.5\mu$  was absorbed from the intestine in amounts comparable with olive oil emulsions of similar dispersion.

Sonnenschein & Ivy (100) confirmed the report of Florey that a humoral mechanism influences Brunner's glands. The transplanted first inch of the dog's duodenum responded to a meal, was practically unaffected by purified secretin, but secreted after in-



jection of crude secretin. Usually, the samples of juice from the jejunum of fasting humans were found by McGee & Hastings (101) to be isotonic with serum. Occasionally, hypotonic juice was obtained, apparently due to admixture with hypotonic solutions from other portions of the gut. Comfort (102) concluded that the duodenal contents of healthy humans are rarely alkaline. When the pH falls below 4, free acid is present, and this condition was encountered in one-fourth to one-fifth of the samples. In duodenal ulcer, the duodenal contents are excessively acid and free hydrochloric acid is encountered more frequently.

*Intestinal motility.*—Van Lier and associates (103) found that anemic anoxia (hemorrhage) depresses the longitudinal colonic musculature in dogs but intestinal propulsion is augmented. Anemic anoxia combined with cocaine administration (104) decreases propulsive motility, due apparently to the potentiating effect of cocaine on the sympathetic nerves. Studying intestinal propulsion by charting the progress of an acacia-charcoal mixture, Stickney, Northrup & Van Lier (105) observed that the hyperglycemia produced by the intravenous administration of glucose significantly retards propulsion. In the experience of Henry *et al.* (106), the prebreathing of oxygen by subjects before decompression to 38,000 feet elevation decreased the incidence of gas pains. The effectiveness of oxygen was proportional to the duration of prebreathing preceding the decompression. Wakim & Mason (107) report that hemorrhage in amounts of 20 per cent of the estimated total blood volume leads to immediate cessation of intestinal activity. Depletion of plasma proteins by repeated plasmapheresis decreases intestinal activity and delays the augmentation of motility normally produced by feeding. However, recovery of intestinal motility occurs before return of plasma protein to the normal level.

Berger & Oppenheim (108) studied the interdigestive discharge of duodenal contents. The intestinal inhibition resulting from intestinal distention is due primarily, according to Youmans (109), to a reflex completed through spinal segments D7 to L2. The thoracolumbar system provides both afferent and efferent pathways for the reflex; apparently, the vagi are not involved. Increasing the distended loop length decreased the minimal pressure required to elicit the reflex and a previous effective distention or a prolonged subthreshold distention produced a peripheral sensitization at the site of the distention to redistention (110).

Zucker (111) apparently demonstrated that the substance in blood serum or in the buffy coat of human blood which stimulates the intestine and other smooth muscle is derived from disintegrated platelets. In isolated segments of rabbit or rat intestine, McClendon (112) found that replacement of 25 per cent of the Ringer's solution with 0.2 *N* sodium acetate augments the motility of both longitudinal and circular muscles. In segments so stimulated, the contractions of longitudinal muscles were abolished by cutting the intestine longitudinally or by turning it inside out. The excised as well as the intact intestine was depressed by sodium secondary-butyl ethyl barbiturate. In the excised intestine this depressant effect was somewhat greater than that of phenobarbital sodium but less than that produced by pentobarbital sodium (113). According to Bauer & Yonkman (114) the sulfur compounds, S-28 ( $\beta$ - $\beta$ -dimethyl- $\gamma$ -4-morpholine-propyl-diphenyl acetate hydrochloride) and S-29 ( $\omega$ -4-morpholine-hexyl diphenylacetate hydrochloride) relieve intestinal spasms, even those produced by morphine. The spasmolytic action of these compounds resembles that of papaverine and nitrites rather than that of atropine, ephedrine, or cocaine. Helm & Ingelfinger (115) noted that in patients receiving the usual preoperative medication, spinal anesthesia does not augment intestinal motility or overcome the effect of moderate doses of morphine and scopolamine. Hazleton & Godfrey (116) stated that the effect of drugs on intestinal motility is analogous when studied by the Sollmann-Rademacker technique or in intact animals. Intestinal loops placed under the dog's skin were inhibited postprandially by amyl nitrite, aminophylline, octin hydrochloride, and trasentine. Demerol produced initially augmented motility, followed by inhibition; papaverine was ineffective (117). Crohn, Olsen & Necheles (118) found that local application of many spasmolytic drugs inhibits intestinal motility (rarely gastric motility), due apparently to anesthesia of sensory receptors and abolishment of local motor and tonic reflexes.

It has been shown by Crender & Wolfgang (119) that histidine, arginine, or cysteine inhibit the stimulating effect of histamine, acetylcholine, or pilocarpine on the excised guinea pig intestine. Histidine or arginine depressed the guinea pig intestine for a brief period. Cysteine depressed after a primary stimulation. Apparently, the inherent depressing effects of the amino acids explain their depression on the actions of histamine, acetylcholine, or pilocar-

pine. These depressions are nonspecific and not entirely dependent on the blockade of -NH receptors by the amino or sulfhydryl group of the amino acids. Enders (120) found that the intravenous injection of sulfathiazole, sulfapyridine, or acetyl sulfanilamide depressed motility and tone of the small and large intestine of the guinea pig. Prostigmine and pilocarpine stimulated motility depressed by the sulfonamides, but *p*-aminobenzoic acid had no antagonistic action on the gut.

Buirge (121) found that the ileocecal valve, the ileocecal sphincter, and the small intestine are all fundamentally similar rather than contrary in their motor activity. The ileocecal sphincter does not show the prolonged tonic contractions supposedly characteristic of sphincter action. Bernthal & Schwind (122) reported that the reflex vascular response to carotid aortic chemoreceptor stimulation is similar in the intestine and the leg, but poststimulation vasodilation occurs in the leg but is usually absent from the intestine. Intense centrogenic and chemoreflex stimulation (prolonged asphyxiation) produce a vasoconstriction of the intestine several times greater than that produced by chemoreceptor stimulation alone.

Wood (123) noted that the surface area per unit length of gut in the rat and cat is greater in the jejunum than in the ileum (due to greater villous development in the jejunum). The ratio of the mucosal area of the entire small intestine to the body weight is similar in the rat and cat. According to King & Robinson (124) the rhythmic movements of the muscularis mucosa are basically myogenic but can be modified by either cholinergic nerves or adrenergic nerves. Herstone & Freund (125) confirmed Mall's report of definite patterns and groups in the small intestine. However, these are not sufficiently constant to permit clinical recognition of the loop. Also, it is impossible to predict the distance of a loop from the duodeno-jejunal junction by its location in the abdomen.

Obstruction of the jejunum of the rabbit was found by Ender & Herrin (126) to increase the blood hematocrit and decrease the plasma volume and the tissue fluid volume. Sodium chloride and water accumulate in the obstructed bowel in sufficient quantities to produce circulatory failure. In the absence of contamination by virulent organisms Spelman (127) found that an anastomosis made in a dog's gut became water tight by development of fibrillar fibrin in fifteen to thirty minutes. Contamination by virulent organisms

results in granular fibrin which tends to pull apart and leak during resolution. Fibrillar fibrin is not formed in the presence of necrotic tissue and adhesions do not form to wall off a gangrenous area. Hollander, Rosenak & Colp (128) have suggested a new synthetic, predigested aliment for jejunostomy feeding. From direct inspection of the rabbit intestine, Auer & Krueger (129) reported that antiperistalsis is associated with a progressive wave of relaxation which precedes the reverse wave of constriction. Thus antiperistalsis obeys the basic conditions described in Bayliss and Starling's Law of the Intestine.

Although irradiation of the duodenum of rats as observed by Friedman (130) inhibits mitosis in the crypts and halts the normal passage of cells up the villi, the maturation of goblet cells is not affected. The ripening of mucous elements while arrested in the crypts, where they form, instead of during their migration along the villi, results in the so-called mucous change, which has hitherto been considered a form of degeneration. During the phase of recovery, the reestablishment of normal migration and desquamation is marked by the appearance of strata of fully formed goblet cells at successive levels out along the villi. Of fifteen dogs with isolated, obstructed high intestinal loops, Harper & Blain (131) found that if untreated, all died within six and one-half days, 87 per cent within three and one-half days or less. In a similar group treated with penicillin, all lived nine days, 93 per cent for thirteen days, and 60 per cent for over a month. Either marked intestinal distention in the presence of bacteriostatic agents, or abundant bacterial flora uninhibited by bacteriostatic agents but without distention is compatible with life.

*Pancreas.*—Cutting or blocking the vagi was found by Crider & Thomas (132) to prevent temporarily the normal response of the pancreas to peptone in the intestine. The response partly returns after twenty-four hours. The response of the pancreas to soap in the intestine is unaffected by vagotomy, and the total nitrogen content of the juice is unaltered regardless of the stimulus. The vagi appear to influence pancreatic juice formation by augmenting or suppressing local reflexes. Splanchnectomy fails to modify pancreatic secretion.

Hart & Thomas (133) were unable to find a relation between the stimulus employed and the concentration of bicarbonate and chloride concentration or the pH of the pancreatic juice secreted.

The bicarbonate and chloride concentrations are reciprocally related and the bicarbonate and chloride vary directly with the rate of secretion at rates below 0.05 ml. of juice per minute per kilo of body weight, but at higher rates they become constant. In trained dogs, Friedman & Thomas (134) found that pancreatic secretion is augmented by peptone, soap, hydrochloric acid, or intravenous secretin. The secretion produced by peptone is of high specific gravity and possesses marked lipolytic and tryptic activity; hydrochloric acid and secretin give a low enzyme content and the specific gravity is also low; that from soap is intermediate in both respects. The relation of enzymatic activity to specific gravity is almost linear.

According to Friedman & Snape (135), all potent secretin preparations also stimulate the liver though not necessarily to the same degree. However, not all intestinal mucosal extracts effective on the liver affect the pancreas. Mucosal extracts apparently yield two substances that affect the liver; one having no effect on the pancreas and another intimately related to or identical with secretin. Munro & Thomas (136) studied the electrophoretic patterns of non-activated pancreatic juice. Five different protein constituents were obtained whose mobilities and relative concentrations were independent of the stimulus or of the total nitrogen content of the juice. In trained dogs, atropine or hyoscyamine decreases the pancreatic response to secretin, soap, or hydrochloric acid. Thus the action of each of these stimuli appears to involve some element of nervous action (137). Stimulation of a dog's pancreas by a single injection of secretin concentrate or by pure secretin produces pancreatic juice in which the first and last portions (especially the former) are of greater density than that flowing when secretion is at its height. This increased density is due to a high concentration of enzyme in the first portion and a low enzyme content in the juice secreted when the flow is maximal. Immediate repetition of secretin injection after a return to the basal rate results in a similar secretory response, but the enzyme content of each fraction is reduced. Repeating the injection several times results in a constant pattern or response in regard to volume and enzyme content of each fraction (138).

Greengard & Ivy (139) extracted from intestinal mucosa a substance, pancreozymin, which is distinct from secretin, cholecystokinin, or vasodepressor substances. In a dog secreting pancreatic juice at the rate of 3 ml. per 15 min. under secretin influence, one

unit of pancreozymin is defined as the amount which would elevate the second three-minute enzyme concentration to the level of the first. In the experiments of Collins & Ivy (140), it was observed that ergotamine or dihydroergotamine markedly diminishes the pancreatic response to secretin but not to prostigmine or epinephrine. Tyrosine production by trypsin from hemoglobin is depressed by detergents according to studies of Block *et al.* (141). Triacetin has a similar effect but the inhibition is less marked if the detergent and triacetin are mixed. Cream and cholesterol act similarly to triacetin.

According to Bells & Schwimmer (142), uncooked starch is readily and completely digested by a mixture of extracts of hog pancreas and "mold bran." Both pancreas and mold bran contain factors (presumably enzymes) which are thermolabile. An inorganic factor present in the ash of wheat flour is necessary for its rapid digestion but this ash factor can be replaced by calcium chloride. Approximately all the starch is converted to sugars. A fundamental difference between the actions of chymotrypsin and trypsin on casein was found by Horwitt (143) in that heparin does not inhibit the activity of the former but strongly inhibits trypsin. Trypsin is precipitated by both hexylresorcinol and heparin; chymotrypsin is precipitated by hexylresorcinol, but not by heparin, while trypsin inhibitor precipitates neither enzyme (144). Aqueous extracts of soy beans or navy beans contain a fraction which inhibits the *in vitro* digestion of milk casein by trypsin. The fraction can be precipitated with acetone. Its presence may account for the low nutritive value of raw soy and navy beans (145).

Ligation of a dog's pancreatic ducts was found by Nothmann (146) to increase the alkaline serum phosphatase in seven of ten animals. Values six to eight times greater than those preceding the operation were obtained. Acid serum phosphatase is not modified by duct ligation. A substance was obtained by Davison & Waymouth (147) from pancreatin which increases the nucleoprotein-phosphorus content of fresh explants of the nine-day chick embryo heart. The effects obtained by the intravenous administration of trypsin indicate that the symptoms observed in acute pancreatic necrosis are not due to the presence of excessive amounts of trypsin in the blood. The phenomena of anaphylaxis apparently are not due to the action in the blood and tissues of trypsin (148). Troll (149) found ectopic pancreatic tissue in two cases of Meckel's di-

verticuli and one case in the ileum. Ectopic gastric tissue was found six times in Meckel's diverticuli and one diverticulum contained both types of tissue. Apparently, the aberrant tissue was transplanted from the original site during embryonic development. Sibley (150) claimed that Meckel's diverticuli should be promptly removed surgically.

Patients with external pancreatic fistulae lose considerable sodium and water according to Wiper & Miller (151, 152). Ephedrine or sodium bicarbonate decreases the flow of juice. The juice resulting from secretin is apparently produced by a filtration process for sodium, calcium, and sulfanilamide; chloride and bicarbonate are present in the same concentration in plasma and in the pancreatic juice. Histamine administered intramuscularly or intravenous saline or glucose greatly increases pancreatic secretion. The prolongation of blood coagulation observed after intravenous injection of trypsin or thrombin into rabbits or dogs was found by Tagnon (153) to be due to diminution of the fibrinogen and the prothrombin of the plasma. Neither heparin nor any other anticoagulant is found in the circulating blood of animals during the shock phase produced by either trypsin or thrombin. The action of thrombin on the blood pressure is entirely abolished by preliminary heparinization and, therefore, is due entirely to its clotting power. The action of trypsin on the blood pressure is not abolished by preliminary heparinization.

Extensive anastomoses were found by Oppenheimer & Mann (154) between pancreatic acinar arterioles and also between recipient capillary regions. Anastomoses existed between intralobular arterioles and also between capillary fields fed by different arterioles within any one lobule. Mirsky & Foley (155) obtained evidence indicating that trypsin inhibitor has antibiotic properties. Cytoplasmic inclusion bodies were found by Duff & Corbett (156) in the acinar cells of the pancreas of mice, rats, and rabbits and in the salivary glands of rats. Apparently they do not result from disease or disturbances of secretory function or dietary factors.

*Colon.*—Comparing the end of a human stool in contact with the rectal mucosa and the end in contact with the mucosa of the sigmoid colon, Steggerda (157) found the content of calcium, phosphorus, and iron in the rectal end to be higher. This indicates the extent of water and chlorine absorption in the rectum. Lieberman (158) emphasized the fact that intestinal gases frequently are com-



bustible, due to the presence of hydrogen and methane and when mixed with air may become explosive. Anderson (159, 160) considered the fat excretion in the feces of normal children, in celiac disease, congenital pancreatic deficiency, and the influence of various diets.

A multiple cassette changer was employed to study colonic motility by Taylor & Hokstra (161). Administration of sodium ketocholocate into the rectum of rabbits or men was found by Dasco, Zeltmacher & Shapiro (162) to produce copious defecation after a short latent period. Steggerda, Taylor & Hokstra (163) studied colonic activity by simultaneously observing the x-ray shadow of the colon wall previously made opaque with thorotrast and the changes recorded by a water manometer when known quantities of gas were introduced into the colon. Pressures measured by water manometers were found by Steggerda, Taylor & Hokstra (164) to be about the same in the proximal and distal colon of dogs. They were unable to show that variations in the amount of gas introduced changed the colonic tone. Application of trypsin to the dog's mucosa produces ulceration according to Portis, Block & Necheles (165). Since trypsin is found in the rectal discharge of patients with ulcerative colitis, the enzyme may be responsible for the lesion. Sodium lauryl sulfate inhibits tryptic activity and may be of value in colitis; however, the presence of foods reduces its effectiveness (165).

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## LIVER AND BILE<sup>1</sup>

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The present review is intended to include only recent studies on the liver and bile not covered by previous reviews on these subjects. Most of the work to be reported was carried out on animals, but relevant clinical observations are also included.

Before reviewing the work on this subject it should be pointed out that there are but a few studies designed to clarify the relation of liver function to appetite. It is a common observation made by experimenter and clinician alike that subjects with liver injury manifest a marked anorexia. Turner and his colleagues (1) were impressed by the constancy of this finding in patients with hepatitis. They attempted to stimulate the appetite by self-selection of foods and found that the patients included in their diets normal amounts of substances rich in butterfat, such as butter and ice cream. Watson (2) has observed that a persistent anorexia in patients with an alcoholic fatty liver is a grave symptom. Protein-deficient dogs generally eat less as their liver function declines. Chemical agents that injure the liver may cause anorexia before liver function tests are altered. Anorexia has been cited as an early and reliable indication of the suppression of cholic acid synthesis in dogs fed cinchophen (3). While it is readily admitted that anorexia is a very general and nonspecific manifestation of deficiencies and ill health, yet it is such a constant accompaniment of liver disease as to suggest that there may be some specific relation between the two. A substance that influences the appetite may be elaborated by the liver.

*Carbohydrate metabolism.*—The formation of glycogen from glucose in fed and fasted rats was studied by Stetten & Boxer (4, 5) who maintained a constant concentration of deuterium oxide in the body fluids and determined the extent to which heavy hydrogen was incorporated into liver and carcass glycogen under various experimental conditions. They calculate the half-life of

<sup>1</sup> This review covers the period from July 1944 to July 1945, but includes some reports published since 1942 which were not summarized in previous reviews.



liver glycogen to be one day and that of carcass glycogen 3.6 days. When rats were well-fed on a high glucose, fat-free diet, only about 3 per cent of the dietary glucose was used via glycogen, and at least ten times as much of the glucose was used for the synthesis of fatty acids as for that of glycogen. The extent of deuterium incorporation in glycogen indicated that liver and carcass glycogen are formed in part from dietary glucose and in part from smaller units. The incorporation of deuterium oxide into the glycogen of fasting rats, and of previously fasted rats fed glucose or lactate, was found to be much more rapid than for well-nourished animals. The glycogen formed in the fasted rat fed glucose was relatively rich in deuterium, a finding which is interpreted as indicating glycogenesis from smaller fragments rather than from dietary glucose directly. The deuterium content of glycogen formed after lactate feeding was compatible with the view that all the hydrogen of the new glycogen was derived from or exchanged with the body water at some time.

In glycogen formed from galactose only about half of the carbon-bound hydrogen was derived from body water, which indicates that lactate is not a major intermediate in the conversion of galactose to glycogen (6). Applying the same technique to a rat with alloxan diabetes, these authors found that the proportion of liver glycogen synthesized from fragments smaller than a hexose was greater than had been found in normal rats, while the synthesis of fatty acids from glucose was greatly reduced in this animal (7).

Buchanan, Hastings & Nesbet (8) used radioactive carboxyl carbon as a marker in studying the conversion of short chain fatty acids into glycogen. Labeled acetic, propionic, and butyric acids were fed with glucose to fasted rats. The radioactive carbon content of the liver glycogen indicated that butyric and propionic acids were converted to glycogen but that acetate was not. Approximately 50 per cent of the radioactive carbon absorbed was excreted in the respiratory gases as carbon dioxide in the two hour period after feeding. No radioactive carbon could be detected in the liver fat two hours after radioactive acetate feeding.

Glycine administration promotes glycogenesis not only from the fed glycine but from other substances as well, according to the results obtained by Olsen *et al.* (9). They found that glycogen formation by mice fed glycine containing isotopic carbon in the carboxyl group was more than could be accounted for by the conversion of glycine to glycogen. Fifty per cent of the isotopic

carbon was recovered in the expired air in a sixteen hour period. The distribution of the nitrogen of glycine was followed by Shemin & Rittenberg (10), who fed the heavy nitrogen as glycine to rats and followed its concentration in various tissue proteins. Their results indicate that half the total protein nitrogen of the liver is replaced every seven days, and that 10 per cent of the liver glycine nitrogen is replaced daily by glycine from other sources.

Treadwell, Tidwell & Grafa (11) found that rats maintained on a high fat, low protein diet had a significantly higher liver glycogen than when the diet was high in both fat and protein. The animals with fatty livers (low protein) had an increased glycogenolysis during fasting and decreased glycogenesis following glucose administration. Soskin (12) has recently reviewed the general role of the liver in regulating the blood sugar level and emphasized the diabetic type of sugar tolerance curve associated with impaired liver function.

The hepatic reserve of glycogen in children has been estimated by Mirsky & Nelson (13) by determining the sugar excretion, hypoglycemia, and ketosis provoked by phlorhizin administration. A loss of 15 to 20 gm. of sugar by a normal child leads to hypoglycemia and ketonemia. Younger children were found to have less glycogen reserve. Dziewiatkowski & Lewis (14) found that glycogen depletion occurs in young well-fed rats four hours after administration of menthol or sodium tertiary butyl acetate. Since these compounds are excreted as glucuronates, it appears probable that glycogen is used as a source for glucuronate synthesis. This relation between glucuronates and glycogen may account for the results reported by Ottenberg and collaborators (15), who found a low glucuronate excretion after borneol administration, not only by patients with liver disease but by patients with other diseases as well.

*Other aspects of liver metabolism.*—Dounce has described an improved method for isolating the intact cell nuclei of rat liver (16). The following enzymes were found in the nuclei: arginase, cytochrome oxidase, esterase, lactic acid dehydrogenase, alkaline and acid phosphatase. The total lipid content of the nuclei was between 10.5 and 11.0 per cent. A heat labile enzyme that catalyzes the decarboxylation of oxalacetic acid was shown by Evans and associates (17) to be present in a cell-free extract of pigeon liver. Woodward (18) found that liver tumors produced by

dimethylaminoazobenzene administration were rich in alkaline  $\beta$ -glycerophosphatase. According to Blaschko (19), liver extracts of the dog, rat, pig, and guinea pig contain an enzyme which forms taurine and carbon dioxide anaerobically from *l*(-)-cysteic acid. Brinkley (20) demonstrated that the liver contains an enzyme which can convert cystathionine (a possible intermediate in the conversion of methionine to cystine) into cystine. Perlzweig *et al.* (21) have shown that the methylation of nicotinamide in the presence of slices of rat liver is an aerobic process which may be enhanced by the addition of methionine. The conversion of methionine into cystine in the presence of liver slices has been demonstrated by Floyd & Medes (22), and the liver enzyme that produces hydrogen sulphide from cysteine has been further purified and characterized by Laurence & Smythe (23).

Oppenheimer & Kunkel (24) demonstrated that the intramuscular injection of uricase from pigs' liver lowered the blood uric acid of "gouty" chickens maintained on a gouty (high protein) diet. Daily injections kept the blood uric acid below the gouty level. Michael, Looney & Borkovic (25) showed that benzoic acid administration led to a decreased uric acid excretion and an increased blood lactic acid during the time when hippuric acid synthesis would be taking place. There was a correlation between sodium benzoate retention and uric acid retention.

Contrary to the general impression, at least some animals appear to be able to metabolize a straight chain saturated hydrocarbon. Stetten (26) found that rats fed 83 mg. per day of a deuterium-containing hexadecane absorbed it efficiently, and that part of it was deposited as such in the tissue fat and part was oxidized to fatty acids, presumably by the liver. Fifteen per cent of the deuterio-hexadecane fed to rats was recovered in the fatty acid fraction.

The experiments of Weinhouse, Medes & Floyd (27) present convincing evidence that the liver can form ketone bodies by condensation of two carbon atom residues derived from the  $\beta$ -oxidation of fatty acids. This appears to substantiate the theory with regard to ketone body formation which has been gaining ground in recent years. *N*-octanoic acid containing heavy carbon in the carboxyl carbon was incubated with liver slices from fasted rats. The acetoacetic acid that was formed contained heavy carbon that was equally distributed between the carbonyl and carboxyl carbons. This distribution can best be explained on the

basis of condensation of two carbon fragments derived from  $\beta$ -oxidation of the *n*-octanoic acid. The fate of three-fourths of the added fatty acid was unaccounted for by this conversion.

Further experiments by these authors (28) indicate that carboxyl-labeled butyric acid is converted to ketone bodies by liver tissue, mainly by fission into two carbon chains with subsequent recombination, but also to some extent by direct  $\beta$ -oxidation of the butyric acid. The classical theory is therefore upheld, and the work of these authors appears to eliminate the need for any theories of fatty acid oxidation other than  $\beta$ -oxidation. In a study of ketone bodies in the tissues of healthy rabbits, Somogyi & Stark (29) found a higher concentration in the liver than in other tissues. In the liver over 90 per cent of the ketone bodies were  $\beta$ -hydroxybutyric acid. The facts suggest that  $\beta$ -hydroxybutyric acid is the mother substance that is formed in the oxidation of fatty acids and amino acids. The reversible conversion to acetoacetic, then, takes place in extrahepatic tissues. That this conversion may also occur in the liver is suggested by the results of Leloir & Muñoz (30) who found that butyrate added to a preparation of liver enzymes was nearly all recovered as acetoacetate; the oxygen uptake by the preparation was much in excess of that necessary for this reaction alone.

Cholic acid and cholesterol containing deuterium have been recovered from the urine of a dog with an internal biliary fistula following the intravenous injection of cholesterol containing the isotope in its ring structure and side chain. Bloch, Berg & Rittenberg (31) found the deuterium concentration of the bile cholic acid and cholesterol similar to that of the blood cholesterol but considerably less than that of liver cholesterol. The closer correlation between the deuterium content of blood cholesterol and bile cholic acid and cholesterol suggests that blood, rather than liver, furnished the precursor of these biliary constituents. However, the total deuterium content of liver cholesterol gives no basis for distinguishing between inert cholesterol stored there following its intravenous injection and that portion participating in the metabolic activities of the liver. Assuming that the deuterium linkage in the ring structure is stable, the experiment clearly demonstrates that cholesterol or some portion of its molecule may be used by the body in the synthesis of cholic acid. The extent to which cholesterol serves as a precursor of cholic acid remains uncertain. Assuming that the blood cholesterol was the immediate

precursor of cholic acid in their biliary fistula dog, Bloch *et al.* calculated that approximately two thirds of the cholic acid originated from the degradation of cholesterol.

Anderson (32) obtained results which indicate that the liver participates in the destruction of quinine by the body. Removal of one third to one half of a rat's liver increased the urinary excretion of quinine 72 to 143 per cent in excess of that excreted when the liver was intact. Damage of the liver of dogs by chloroform permitted a high blood quinine for a longer period of time and also caused an increased urinary excretion.

*Fatty livers.*—McHenry & Patterson (33) have recently published a review of lipotropic factors, including choline, lipocaic, and inositol.

Stetten & Salcedo (34) have presented evidence as to the source of extra liver fat in various types of fatty livers. Rats were maintained on a fat-free diet, and the newly synthesized fatty acids were labelled with deuterium by enriching the body fluids with deuterium oxide. The deuterium content of liver and storage fat was then determined. The results obtained by this technique indicate that the fatty livers in choline deficiency are due to impaired fatty acid transport from liver to depots. The fatty livers after cystine [as after thiamine (35)] administration are associated with an increased rate of fat synthesis, while anterior pituitary extract injected into fasting mice caused an excessive mobilization of depot fat and its migration to the liver. The results lend support to the belief that the liver is the major site of fatty acid synthesis.

Stetten & Salcedo (36), in accord with the earlier observations of Channon and collaborators that the severity of fatty liver in choline deficiency was influenced by the nature of the dietary fat, further report that when each of the even numbered fatty acids from butyric to stearic was fed as an ethyl ester to rats receiving no choline, a marked increase in fatty livers occurred with decreasing chain length of the dietary fatty acids from eighteen to fourteen carbon atoms, but that no severe fatty livers were encountered after feeding fatty acids of less than twelve carbon atoms.

The effect of dietary choline upon the rate of turnover of phosphatide choline was studied by Boxer & Stetten (37) by means of choline containing heavy nitrogen. When choline was fed, the half life of phosphatide choline was six days. When no choline was fed the half life of the phosphatide choline increased to

eighteen days during the development of fatty livers. From these results it is apparent that choline privation retards the rate of introduction of choline into the phosphatides of the body without altering the amount of choline in the phosphatides. It would appear from this study as well as from the work of Perlman & Chaikoff (38) that the effect of choline upon the development of fatty livers is related to the rate of turnover of the choline phosphatides.

Fishman & Artom (39) demonstrated that the decrease in liver lecithin produced in weanling rats by a protein-deficient diet could be corrected by choline, and that ethanolamine, *dl*-methionine, *dl*-serine, and glycine did not duplicate the effect of choline, although ethanolamine alone or with methionine had some effect. The effectiveness of choline was largely lost in somewhat older rats after they were maintained on the experimental diet for seven days.

The lipotropic effect of various intraperitoneally injected sulphur compounds has been studied by Roberts & Eckstein (40) using a low-protein, high-fat diet and paired feeding technique. They studied dimethyl disulphide, dimethylsulphide, S-methyl isothiouraea, methyl xanthogenate, methionine sulfone, and trimethyl sulfonium chloride. The first four mentioned compounds all exerted a lipotropic action and all could give rise in the body to methyl mercaptan.

The influence of other essential amino acids in the diet upon the lipotropic effect of methionine has received recent emphasis. Channon and co-workers (41) demonstrated that there was some substance, other than cystine, methionine, and tyrosine, affecting liver fat in the butanol-soluble fraction of a protein digest. Beveridge *et al.* (42) found that, if the other essential amino acids were present to the same extent, the lipotropic action of methionine was the same, whether it was fed as the free amino acid or in a casein hydrolysate. On the same subject, Treadwell *et al.* (43) demonstrated that the availability of methionine for lipotropic action depends upon the other amino acids in the diet. This point was well illustrated by the fact that rats fed 20 per cent arachin and 0.5 per cent methionine grew normally but developed fatty livers. An increase of the methionine to 1 per cent permitted normal growth, and the livers were only slightly fatty.

A relation of growth to the development of fatty livers in rats was clearly illustrated by Handler (44) who showed that simulta-

neous mineral and choline deficiencies prevented growth and fatty infiltration of the liver. The choline-deficient rats receiving minerals grew and developed fatty livers, even though the diet was restricted to the same degree as for the group with both choline and mineral deficiencies.

Beveridge & Lucas (45) found that corn oil obliterates the lipotropic effect of inositol in rats fed a purified diet low in sulphur-containing amino acids and fat and high in carbohydrate. Under the conditions of their experiments, choline caused a much more marked reduction in the cholesterol ester content of the liver than did inositol.

Montgomery and collaborators (46) found the feeding of raw pancreas to depancreatized dogs for the first few weeks after pancreatectomy to be without significant effect upon the final fat content of the liver (17 to 53 per cent) when they were maintained on insulin for fifteen to twenty weeks after discontinuation of raw pancreas feeding. These authors (47) also report the lipocaic is relatively ineffective in preventing fatty livers in completely depancreatized dogs maintained on insulin. Entenman *et al.* (48) have described the preparation of a pancreatic fraction that prevents fatty livers in depancreatized dogs. It is prepared by precipitation of an acid extract of pancreas with a concentration of ammonium sulphate between 0.25 and 0.5 saturated. Sixty milligrams daily of this fraction maintained a normal liver fat in depancreatized animals for as long as six months.

Ariel and colleagues (49) have shown that patients with gastrointestinal malignancy very frequently have fatty livers. According to Abels *et al.* (50), inositol is more effective than either choline or lipocaic in reducing the liver fat of these patients. They ascribe the lipotropic properties of lipocaic to its inositol content.

Winkler *et al.* (51) have shown in the monkey and dog that bilateral nephrectomy or ureteral ligation results in lipemia, a marked increase in liver phospholipids, and a less striking rise in liver cholesterol. These changes are not prevented by glucose administration nor do they follow unilateral nephrectomy, splenectomy, or fasting.

Karsner (52) has recently written an interesting account of morphology and pathogenesis of cirrhosis of the liver as seen in man. The experimental production of liver injury and cirrhosis by dietary means has been reviewed by György (53). The pigment, ceroid, which has been found in the livers of rats with dietary



cirrhosis has been further characterized and differentiated from other pigments by Endicott & Lillie (54). Popper, György & Goldblatt (55) have also studied this substance, which they describe as a golden brown fluorescent material which develops in the cell containing fat and remains there after fat removal as morphologic evidence of a disturbed fat metabolism. That some particular constituent of fat may be essential to ceroid formation is indicated by the finding of Endicott, Daft & Sebrell (56) that dietary cirrhosis can be produced in rats without ceroid by proper selection of the diet. Their results indicate that some substance contained in cod liver oil may generate the pigment. They also demonstrated that cirrhosis can be produced on a fat-free diet.

Himsworth & Glynn (57, 58) report production of massive necrosis of the liver of rats on a diet deficient in protein. This they could prevent by 8 per cent casein or by the amount of methionine contained in 8 per cent casein but not by cystine or choline. Cirrhosis of the liver which was also produced by a protein deficient diet they ascribe to long continued heavy fat infiltration of the liver. A distinction is made between the lesions that lead to massive necrosis and to cirrhosis; the former condition is regarded by some as a stage in the development of cirrhosis.

Fatty infiltration of the liver and portal cirrhosis have been found by Chaikoff *et al.* (59) in dogs deprived of both pituitary and thyroid glands for 70 to 419 days. Cirrhosis of the liver in donor dogs subjected to repeated plasmapheresis for one to three years and fed a high fat diet has been reported by Holman (60).

*Liver injury by various agents.*—Berryman & Bollman (61, 62) have shown that immature rats maintained on a restricted diet and exposed to carbon tetrachloride showed a decrease in plasma protein concentration, which is largely due to hypoalbuminemia. A comparable dietary restriction produced no such lowering of plasma proteins in the control group. The plasma protein level of the exposed group varied with the protein intake but was uninfluenced by partial substitution in the diet of proteins of widely varying plasma protein regenerative value. These results indicate that the functional capacity of the liver to form plasma protein was the limiting factor in determining their concentration rather than the protein intake. Pregnant rats exposed to carbon tetrachloride also showed a decrease in plasma proteins as compared to unexposed paired controls.

Rats maintained on a high fat diet and exposed to trinitrotol-

uene developed necrosis and fatty infiltration of the liver. Hims-worth & Glynn (63) believe that the high fat intake reduced the animals' ability to dispose of trinitrotoluene. However, it should be pointed out that their high fat diet furnished considerably less protein per one hundred calories than did the other diets studied. A marked increase in the susceptibility of dogs to chronic benzene poisoning has been produced by Li *et al.* (64) by restricting the protein intake. The fat content of the diet did not have a definite effect upon the dog's susceptibility to benzene. Fatty livers reduced Rose Bengal dye clearance, and elevation of serum phosphatase were more marked in exposed animals than in their controls. Enlargement of the liver and macrocytosis were noted by Greenburg *et al.* (65, 66) in 106 painters exposed to toluene fumes (one hundred to eleven hundred parts per million) for periods of time ranging from two weeks to five years. Morrison (67) has studied the effect of various anesthetics on the bile salt excretion in patients with surgical drainage of the biliary system. Ether anesthesia, rectal avertin, and chloroform, as used in obstetrics, all caused temporary hepatic dysfunction while sodium evipan, cyclopropane, and nitrous oxide had no effect on bile salt output. Evans *et al.* (68) found relatively little histological evidence of liver injury in mice exposed to isopropenyl vinyl ether.

Goodell *et al.* (69) found that protein depletion increased the susceptibility of dogs to hepatic injury by mapharsen. The tolerance of the protein-depleted animals for this arsenical was increased by adding 2 to 4 gms. of methionine to the diet on the day prior to arsenic injection. Beattie (70, 71) found that a man poisoned by carbon tetrachloride ingestion and treated with methionine and casein hydrolysate injections had a delayed and reduced sulphur excretion in the urine at the time of hepatitis as compared to the excretion six months later when the recovered patient received similar injections. Shaffer & Critchfield (72) found an increase in the sulphur and nitrogen content of fat-free liver tissue from rats exposed to carbon tetrachloride for two weeks and maintained on an adequate protein intake. They believe that the protective effect of methionine or protein against chlorinated solvents is due to its lipotropic effect and not to any other more specific protective property.

Mirsky *et al.* (73) found the cephalin-cholesterol flocculation test positive in ten cases of malaria of varying duration. Guttman *et al.* (74) found that in malarial infection the serum protein content

is more deranged than many liver functions, and that the cephalin-cholesterol flocculation test reflects these changes. From electrophoretic studies they believe that the positive cephalin-cholesterol flocculation test in malaria is probably due to: (a) hypoalbuminemia, (b) a decreased capacity of the serum albumin to inhibit the flocculating action of gamma globulin, and (c) an increase in the gamma globulin content of the serum in this disease. Areas of necrosis in the livers of rats fed atabrine have been reported by Wright & Lillie (75) and by Scudi & Hamlin (76). Silber, Clark & Siegel (77) found an elevation of plasma fibrinogen as well as liver necrosis in rats fed atabrine. They found that an atabrine concentration of 5  $\mu$ g. per cc. in the blood of a 120 gm. rat produced gross necrosis of the liver in five weeks. Annegers *et al.* (78) did not observe any marked or consistent depression of cholic acid output in bile fistula dogs fed 100 to 150 mg. of atabrine daily for one week, although this function of the liver was temporarily impaired in some animals. McCorkle (79) determined the hippuric acid excretion on fifty-five cases of malaria before and after treatment with atabrine. Eight of the patients had an initially low hippuric acid excretion which was improved in most instances after twelve days of treatment with large doses of quinine and atabrine. As judged by hippuric acid excretion, the hepatotoxic action of atabrine was insignificant.

Smith and collaborators (80) found that a diet rich in protein will protect the liver of rats from structural or functional damage by certain azo dyes. Whole liver extract according to Chamelin & Funk (81), reduced the mortality of rats receiving toxic doses of diethylstilbestrol or sulfanilamide from 50 to 25 per cent and diminished the weight loss of the survivors. Forbes & Evans (82) found that orally administered sulfanilamide reduced the toxicity of chloroform in dogs and rats. Dillard *et al.* (83) report that glucose or sucrose administered after chloroform anesthesia reduced or prevented fatty infiltration of the liver. Sugar administered prior to anesthesia had no effect on the subsequent development of fatty livers.

It has been adequately established experimentally that tannic acid can injure the liver. Cameron *et al.* (84) found that tannic acid injected subcutaneously or intravenously into experimental animals caused, among other effects, necrosis of the liver. The tolerance of rabbits for galactose was reduced by tannic acid injection, according to Clark & Rossiter (85). A positive test for tannic acid

was obtained by Barnes & Rossiter (86) on liver tissue from guinea pigs after the application of tannic acid to surface burns covering one-third of the body; histological evidence of liver damage was greater in the treated guinea pigs than the similarly burned control animals. Baker & Handler (87) as well as Cameron *et al.* (84) demonstrated that the toxicity of tannic acid is not due to gallic acid. All the astringent treatments of burns (tannic acid, silver nitrate, and ferric chloride) cause liver necrosis according to Hartman & Romever (88). Forbes & Evans (89) found that neither sulfanilamide nor xanthine protected the liver against subcutaneously injected tannic acid.

Suppression of cholic acid synthesis by cinchophen in dogs with bile fistulas has been demonstrated by Annegers *et al.* (3) under experimental conditions that permitted the enterohepatic circulation of cinchophen. The suppression of bile acid synthesis and secretion may occur in susceptible animals in the absence of anorexia or gastroenteritis. The authors believe that this effect is due to the direct action of cinchophen on the liver. From these and previous results it appears that in certain instances the response to a given dose of cinchophen is unpredictable in dogs just as it is in human beings.

Irish & Jacques (90) found that small intravenous doses of dicoumarol increased the plasma fibrinogen of fasting dogs while larger doses depressed its concentration. These results are similar to those obtained with liver toxins and the authors believe that the response of fibrinogen is evidence of mild or severe liver injury by dicoumarol. Emmel & Dam (91) obtained no histological evidence of liver damage in chickens fed 0.25 to 1.0 mg. per gram body weight of dicoumarol daily for one to five days.

*Vitamin content of the liver.*—There is evidence (92 to 95), obtained on chickens and dogs, that the liver contains unidentified factors that have to do with feathering, blood formation, growth, and color of the hair. The liver fails to retain riboflavin if rats are maintained on a protein-deficient diet according to Unna *et al.* (96). Singher *et al.* (97) found that a deficiency of either riboflavin or thiamine caused a marked increase in the liver content of the other vitamin. Wright & Welch (98) demonstrated that the storage of folic acid and biotin by the liver was less on a synthetic than on a stock diet and that the addition of succinylsulfathiazole to the synthetic diet further reduced hepatic storage of these factors and of pantothenic acid. Feeding, or parenteral administration, of

pantothenic acid to these animals did not relieve signs of its deficiency or replenish the depleted liver store of this vitamin unless biotin and folic acid were also administered.

Clayton & Bauman (99) found that the rate of depletion of vitamin A from the liver of rats on a vitamin A-deficient diet was uninfluenced by *p*-dimethylaminoazobenzene, 4-hydroxycoumarin, fat, and choline. Callison & Knowles (100) found that the liver vitamin A stores of rats are practically exhausted before hemeralopia appears. Females were more readily depleted of vitamin A than males. Fifty to eighty units of vitamin A per kg. were required before storage in the liver occurred. The authors believe that liver storage occurs in the normal animal only after some considerable need of the body has been met.

*Inactivation and excretion of hormones by the liver.*—Both *in vitro* and *in vivo* studies have been made on the inactivation and excretion of natural and synthetic hormones by the liver. The rapid disappearance of  $\alpha$ -estradiol from rat liver perfusate was demonstrated by Schiller & Pincus (101, 102). They suggest that the liver may be concerned in the normal conversion of  $\alpha$ -estradiol to estrone and estriol. The latter compounds can be recovered from the urine after injection of the former one. Heller (103) also perfused rat livers with  $\alpha$ -estradiol and attributed its rapid disappearance from the perfusion fluid to oxidative destruction. Cantarow *et al.* (104) could not recover the active estrogen from the liver three to forty-eight hours after the intravenous injection of 250,000 I.U. of  $\alpha$ -estradiol into dogs. There were large amounts of gallbladder bile twenty-four to forty-eight hours after injection but none in the liver, spleen, intestinal wall, or hepatic vein blood. The *in vitro* inactivation of  $\alpha$ -estradiol by liver tissue from rats poisoned with carbon tetrachloride was also demonstrated. These authors suggest that the estrogen is removed from the blood by liver cells, temporarily stored in an inactive form, and then reactivated and excreted in the bile to undergo an enterohepatic circulation similar to that of bile salts. Comparative data (105) on the biological assay of estrogenic activity and chemical estimation of estrogenic material contained in dogs' bile following intravenous  $\alpha$ -estradiol injections has yielded results which are not in good agreement and necessitate further study of this question.

Segaloff (106) found that there was less inactivation of diethylstilbesterol and hexasterol after their intrasplenic injection than following similar injections of estrone and  $\alpha$ -estradiol. Stilbesterol

is inactivated *in vitro* by liver pulp but less readily than estrone according to Zondek, Sulman & Sklow (107). This finding substantiates the opinion that differences in oral effectiveness of various estrogens may be attributed to differences in the rate of inactivation by the liver. A relatively greater resistance of the artificial estrogens to hepatic inactivation was also reported by Lipschultz and colleagues (108), who found that intrasplenic or intrahepatic pellets of artificial estrogens produced abdominal fibroids and other toxic manifestations not seen with pellets of natural estrogens. Further studies by Lipschultz *et al.* (109) with natural and artificial estrogens indicate that urinary estrogens, or their derivatives, are inactivated by the liver. However, Cantarow *et al.* (110) suggest that estriol and equilin are merely excreted in the bile and probably do not undergo enterohepatic circulation. Kochakian *et al.* (111) implanted pellets of progesterone at various sites in the rabbit's body and judged their progesterone activity by changes in the uterine horn. The results indicate that the liver is the principal site of inactivation of this hormone.

Szego & Barnes (112) found that the accumulation of dietary fat in the livers of mice did not impair the mechanism for detoxifying estrone as judged by their sensitivity to this substance. Segaloff & Segaloff (113) found that the administration of thiamine and riboflavin to B-complex-deficient rats restored the liver's ability to inactivate estrone and  $\alpha$ -estradiol. The thiamine effect was not due to a restoration of appetite, although both inanition and B-complex deficiency decrease the ability of the rat's liver to inactivate diethylstilbesterol. According to Singher *et al.* (114), liver slices from thiamine- and riboflavin-deficient rats do not inactivate estradiol under conditions in which control slices possess this activity. Deficiencies of pantothenic acid, pyridoxine, biotin, and vitamin A had no effect on estradiol inactivation under similar conditions. Dietary cirrhosis impaired the ability of rats to inactivate estrone, according to Shipley & György (115). Unna *et al.* (116) found that addition of methionine to a protein-deficient diet restored the ability of liver slices to inactivate estradiol.

Schiller & Pincus (117) found that partial hepatectomy increased the urinary excretion of endogenous estrogen in rats, and that 65 per cent of injected estrone could be accounted for in the urine metabolites. Their results indicate that partial hepatectomy interferes with the conversion of estrone to estriol. Fels & Eaudi (118) report that removal of 50 per cent or more of the liver leads

to abortion in rats, while removal of one-third or less is without effect. Pregnancy was possible again nine days after a partial hepatectomy that previously produced an abortion. Desoxycorticosterone or progesterone did not prevent abortion in partially hepatectomized animals.

Additional experimental evidence showing that endogenous androgens are inactivated by the liver is supplied by the experiments of Krichesky *et al.* (119) who found that prostatic implants would not take when the testes of rabbits were implanted intra-mesenterically and the original circulation severed. However, when an anastomosis between the implanted testes and the abdominal wall was established, the prostatic implants grew.

The biliary excretion of both androgens and estrogens following the intravenous injection of androsterone, testosterone, or methyl testosterone was reported by Paschkis *et al.* (120).

Castration reduced the number of binucleated liver cells, while estrogen, progesterone, and sesame oil increased the incidence of such cells in normal and castrate rabbits, according to Allan (121).

Eversole & Gaunt (122) found that the effectiveness of desoxycorticosterone acetate in maintaining adrenalectomized rats was reduced by absorption into the hepatic portal system, when administered either in food or as implanted pellets. This reduction in activity they ascribe, as have others, to greater inactivation by the liver.

*Liver function tests.*—Newly born infants excrete bromsulfalein at a rate similar to that of adults. Salmon & Richman (123) found no correlation between the icteric index and rate of dye excretion. Some infants and their mothers have positive cephalin flocculation tests during the first week of the child's life, after which the test becomes negative. There was no consistent relation between the icteric index and cephalin flocculation test or between the hematocrit and icteric index.

Li *et al.* (124) produced a chronic hyperbilirubinemia in dogs for four weeks by repeated injections of a suitably prepared bilirubin added to plasma. The dogs remained in good health, although the Rose Bengal clearance was approximately 55 per cent of normal. Hough *et al.* (125) were able to delay for several weeks the manifestations of impaired liver function in dogs on a protein-deficient diet by adding 0.5 gm. of choline chloride to the diet daily. Cystine had the opposite effect to choline, making the dye clearance less and the serum phosphatase higher. Puppies on a choline-



deficient diet low in methionine also had a reduced dye clearance and elevated serum phosphatase; oral choline prevented or reversed these changes. Similar changes in choline-deficient puppies were obtained by McKibbin, Thayer & Stare (126), who further demonstrated a decreased plasma cholesterol, increased prothrombin time, anemia, and hypoproteinemia. Adding choline to the diet restored liver function in five to ten days (127).

Drill & Ivy (128) found that in dogs given carbon tetrachloride the bromsulfalein test became positive first, next the serum phosphatase rose, while prothrombin time and intravenous galactose tolerance changed last or remained normal. Loomis & Quick (129) gave dogs chloroform or hydrazine sulphate and found that the plasma prothrombin level became abnormal more readily than glycuronic acid excretion or plasma fibrinogen. Glucose and glycine failed to hasten recovery of these animals. That the "most sensitive test" of altered liver function varies greatly in different conditions is further illustrated by the finding of Drill *et al.* (130) that cholecystectomy caused a rise in serum phosphatase while bromsulfalein clearance remained essentially normal.

The ingestion of 4 gm. of tyrosine causes an elevation in its blood level in the normal person, but this increase is much prolonged in the person with liver disease. Bernhart & Schneider (131) state that the response to ingested tyrosine is a more sensitive test of liver function than bromsulfalein or other common liver function tests.

In the initial stages of hepatic injury, the ingestion of considerable quantities of water causes an early and excessive diuresis, while in more advanced damage diuresis is delayed and diminished. Aldersberg & Fox (132) have demonstrated this relationship in the dogs poisoned with phosphorus and in human subjects with arsenical hepatitis. It has been suggested by Shay *et al.* (133) that impaired liver function accounts for the abnormal retention of water by rats fed a high fat diet.

Some delay in the complete removal of intravenously injected casein digests from the blood of patients with liver disease has been demonstrated by Lyttle *et al.* (134), who suggest that this finding may be due to a reduced rate of deamination by the liver.

Moore *et al.* (135) have correlated the results of the cephalin-cholesterol flocculation test in patients with hepatitis with the concentration of the various serum proteins as determined by elec-

trophoresis. Their results indicate that serum albumin inhibits flocculation while gamma globulin causes flocculation.

A new test for liver dysfunction has been described by MacLagan (136), who observed that sera from patients with liver disease became turbid in the presence of thymol or certain phenolic compounds. The principle involved appears to be the same as for the cephalin-cholesterol flocculation or colloidal gold tests. The thymol turbidity test was positive in 120 out of 130 cases of infective hepatitis and only weakly positive in three out of thirty-eight cases of obstructive jaundice. The author believes the thymol test to be more specifically related to liver dysfunction than is the colloidal gold test. Najjar *et al.* (137) have suggested the methylation of nicotinamide as a measure of liver function. Following the blood vitamin A level of patients with liver disease may be of prognostic and diagnostic value, according to the results reported by Adlersberg *et al.* (138). They make the interesting suggestion that the liver controls or correlates the complicated enzymatic systems concerned in the absorption of fats and fat soluble vitamins.

According to Hoffbauer (139), needle biopsies indicate that altered function tests and anatomic changes do not necessarily follow a single pattern. Cirrhosis of a similar anatomical extent may be associated with different types and degrees of functional impairment of the liver.

Studies of liver function tests could be made more comparable and valuable if the diets were of known composition. Carbohydrates, fats, proteins, vitamins, and calcium have all been shown, under certain circumstances, to influence the function of the liver and its tolerance to injurious agents.

*Hepatectomy, circulation, perfusion, and regeneration.*—Berryman, Bollman & Mann (140) found that some globulin was added to the circulation after hepatectomy whether or not plasmapheresis was also instigated. Animals with Eck fistulas or previously damaged livers did not add globulin or added it only in diminished amounts. The immediate changes in concentration of plasma proteins after complete removal of the liver were found to be a small decrease in total protein and albumin, a marked loss of fibrinogen and euglobulin, and an increase in pseudoglobulin of the plasma. Up to thirty hours after hepatectomy there was little evidence of the addition of protein to the plasma. Whipple *et al.* (141) find that dogs with Eck fistulas cannot utilize their diet and iron as effi-

ciently as normal dogs as judged by the production of hemoglobin and plasma proteins. Bleeding or plasmapheresis was followed by a low production of plasma proteins. These authors believe that the liver is concerned directly or indirectly in the production of new hemoglobin. These authors also found that the Eck fistula dog has a higher tolerance for chloroform than has a normal animal.

Roberts, Samuels & Reinecke (142) found that the food predominantly burned after evisceration corresponded to the major constituent of the preceding diet as judged by oxygen consumption. This finding applied to high fat as well as high carbohydrate diets and indicates that fat utilization occurred in the absence of the liver.

Engel *et al.* (143) found that the livers of rats tolerated anoxia up to 45 minutes but that longer periods caused irreversible damage. The high blood amino nitrogen found in hemorrhagic shock was explained as due to a poor circulation to the liver or impaired liver function secondary to anoxia. Harkins *et al.* (144) determined the effect of altered blood flow through the liver and intestines upon the azotemia resulting from blood in the small intestine. The azotemia was greatest in animals with a reverse Eck fistula; there was a lesser increase after ligation of both portal vein and vena cava or in normal animals; and the azotemia was inappreciable in animals with Eck fistulas or in those in which a total hepatectomy had been carried out. These results suggest that the azotemia is related to blood flow through the liver. More direct information on the role of the liver in this process might be obtained from dogs with London cannulas on the portal and hepatic veins. The nitrogen fractions of these bloods could be determined simultaneously and the addition or removal of nitrogen by the liver made apparent.

Wakim (145) transilluminated the livers of frogs and rats to observe the effect of various substances on the intrahepatic circulation. Glucose, particulate matter, India ink, and dyes increased intrahepatic circulation, and the Kupffer cells rapidly became loaded with these substances, with the exception of glucose. Thyroxine produced a marked increase in vascular activity so that most of the sinusoids were in the active phase, while epinephrine produced blanching of the liver by causing constriction of intrahepatic vascular ramifications. Acetylcholine had no perceptible vasodilator effect. Patek (146) could not demonstrate specific lymphatic pathways through the liver lobule when dyes were in-

jected into the blood stream. Lymphatics leaving the liver were colored but there was no streaming of the dye as it diffused from sinusoids to lobule. Further evidence that there is a streamline flow of blood into the liver has been presented by Hahn *et al.* (147). Following intrasplenic injection of radioactive phosphorus it was demonstrated to be in highest concentration in the left part of the liver, while the right side of the liver had the highest concentrations following injections into mesenteric vessels.

Shafiroff *et al.* (148) have studied the acute effect of altered blood flow through the liver upon the bilirubin content of blood and thoracic duct lymph in dogs with a biliary pressure equal to 300 mm. of water. Ligation of the hepatic artery or Eck fistula formation reduced the bilirubin content of the blood and lymph, while an increase resulted from denervation of the liver, formation of a reverse Eck fistula, or obstruction of the hepatic veins. These findings and previous work by the same group indicate that the intrahepatic resorption of bile is influenced by both vascular and biliary pressure in the liver.

Rostorfer *et al.* (149) have described an apparatus for perfusion of the liver in a closed system which permits one to measure the loss of gases from the surface of the liver. The authors point out that this loss may account for some of the low respiratory quotients reported for the liver. A simple technique for circulatory exclusion of the liver in a study of hepatic function has been described by Grande Covian & de Oya (150). The hepatic artery of a heparinized animal is ligated and the portal blood diverted to the external jugular vein by an external system of cannulas and tubes.

Marshak & Walker (151) have studied the effect of various liver fractions upon mitosis in regenerating liver. Intravenous injections of chromatin, fat-free chromatin, or the fraction of chromatin soluble in molar sodium chloride all increased mitosis in regenerating liver. Other fractions of liver inhibit mitosis. Amino acids, nucleic acid, lipids, biotin, adenosinetriphosphate, and insulin either had no effect or an inhibitory one on mitosis. They also found (152) that there is a remarkably rapid uptake by the liver nuclei of intravenously injected particulate materials derived from chromatin and labelled with  $P^{32}$ .

#### BILIARY SYSTEM AND BILE

The usual terminology employed to describe the formation, flow, and characteristics of bile is full of ambiguity because of

varied usage. A somewhat different terminology, employing terms which are used to some extent already, has been defined by Ivy (153). According to this terminology, cholepoiesis is the appropriate term to connote the process of bile formation by the liver. Cholanopoiesis refers to the synthesis of cholic acid. A cholecystogogue is an agent that causes evacuation of the gall bladder, while cholecystokinetic refers to the property of causing the gall bladder to contract.

Boyden *et al.* (154) studied the bile flow and gall bladder evacuation in medical students after instillation of 30 cc. of saturated magnesium sulphate into the duodenum. Changes in volume of the gall bladder were computed from the x-ray shadows and the results obtained compared with those previously obtained with egg yolk. These two agents, one ordinarily considered as a cholecystogogue and the latter recognized as a cholecystokinetic agent, were found to act for the same length of time and to have the same qualitative effects on the gall bladder and sphincter of Oddi, differing only in that egg yolk had a somewhat greater effect. The authors believe that magnesium sulphate should be considered as a hormone-producing substance, the hormone acting independently through the blood stream on both gall bladder and sphincter. If such is the case it should be possible to obtain more direct evidence that magnesium sulphate in the gut causes active contractions of the gall bladder.

A detailed anatomical study of the blood supply and innervation of the choledochoduodenal junction of the cat has been published by Schulze & Boyden (155). Johnson & Boyden (156) studied the function of the two nerve pathways to this area in the cat. Severance of one pathway, the gastroduodenal plexus, had no effect on the emptying time of the biliary tract, while section of the other, the gastroduodenal nerve (right vagus), markedly retarded its emptying. Section of the right vagus, and its celiac division, produced even greater delay in the flow of bile, from which it was inferred that the right vagus not only sends inhibitory fibers to the sphincter but motor fibers to the gall bladder via the hepatic plexus. Section of the left vagus, which sends fibers to the gall bladder but not to the choledochoduodenal junction, also retards emptying of the gall bladder but to a lesser degree. It was also shown that pain impulses from the cecum which retard emptying of the biliary system enter the cord as low as the second lumbar sympathetic ganglion. Boyden & Van Buskirk (157)

demonstrated that section of all the extrinsic nerves to the sphincter of Oddi, although destroying the preganglionic fibers, does not cause the ganglion and post-ganglionic fibers to the sphincter to degenerate. The authors suggest that it is this intrinsic nerve network (which they demonstrate) that continues to respond to hormonal stimuli after both vagi and splanchnics are sectioned.

Gray *et al.* (158) divided the sphincter of Oddi and found that bile collected from a cannula in the gall bladder contained diastase, whereas dog bile is normally free of this enzyme. That an incompetent sphincter permits a reflux of duodenal contents into the common bile duct and gall bladder is indicated by these results.

Urobilinogen, which is normally absent in fresh human bile, was found by Jankelson (159) in the bile of 50 per cent of patients with organic liver or biliary tract disease.

Nesbitt (160) has correlated the urinary excretion of coproporphyrin III with the renal and hepatic function of patients with alcoholic cirrhosis. During acute episodes of hepatic insufficiency the urine volume and coproporphyrin excretion both decline. The same author (161) has demonstrated the urinary excretion of coproporphyrins I and III by patients with hepatic damage or obstruction during maintenance on a porphyrin-free diet. These compounds, which arise during the synthesis of hemoglobin, had been recovered previously from the urine of healthy persons, but in these persons they could have had a dietary origin since the subjects were not on a meat-free diet.

Tat, Greenwalt & Dameshek (162) found that the fecal bilirubin of thirty normal infants ranged from 1 to 23 mg. per day (average, 8.6) during the first five post-natal days; during the five day period it ranged from 0 to 16 mg. (average, 5.7), and from the tenth to fifteenth day the average was 5.3 mg. During this time fecal urobilinogen values ranged from 0 to 0.7 mg. per day. Bilirubin disappeared from the stools eight to seventy-five days after birth, and urobilinogen could usually be demonstrated in the stools during the first week of life. The fecal urobilinogen of children seemed disproportionately small as compared to that of the adult. The excretion in children under two years was 2.5 mg. daily, from three to eleven years 2.7 mg., while the normal adult excretes 50 to 200 mg. per day. Similar results on normal infants have been reported by Boswell & Fielder (163).

The injection of penicillin into man was followed by its appearance in bile in concentrations somewhat higher than in the blood, according to Rommelkamp & Helm (164). A similar relation between the sulfapyridine content of blood and bile was demonstrated by Gough (165). Following obstruction of the cystic duct of dogs, Lynn *et al.* (166) were unable to demonstrate any sulfa drug in the gall bladder bile, although a high blood concentration was maintained for as long as two days. However, simple obstruction of the cystic duct can hardly be considered as analogous to acute obstructive cholecystitis, which the authors state is uninfluenced by sulfa drugs. In the former instance absorption from the gall bladder would continue, while inflammation of and exudation into the gall bladder characterizes the latter condition.

Very little iron, some cobalt, and 50 to 75 per cent of manganese are excreted in the bile of dogs when intravenously injected according to Greenberg *et al.* (167), who used radioactive elements to follow their biliary excretion. Libet & Elliott (168) found that intravenously injected radioactive iron can be recovered from the liver in the form of an iron-protein complex "ferrin." They have prepared an iron-protein complex from the liver of all the animals thus far tested. The yield from pigs' liver was 48 mg. per 100 gm. of dried liver. Using radioactive iron as a tracer, Granick & Hahn (169) also found that injected iron rapidly accumulates in the dog's liver and that 80 per cent of the iron of ferric ammonium citrate can be recovered from the "ferratin"-rich fraction of the liver thirteen days after its injection. Macklin has raised the question as to whether or not iron is stored normally in large quantities in human fetal livers. In 60 per cent of 139 fetal livers no iron could be demonstrated by the Prussian Blue technique. He suggests that when iron can be demonstrated by this technique in the fetus it indicates undue hemolysis in the fetus, which is probably due to incompatibility with the maternal circulation.

Only 15 per cent of atabrine administered to dogs could be recovered in the bile of biliary fistula animals by Annegers *et al.* (78). Forty-three per cent of an average dose of cinchophen was excreted in the bile of biliary fistula dogs in twenty-four hours. Annegers *et al.* (170) found that a moderate choleresis will increase cinchophen excretion in bile, but a limit is reached beyond which further choleresis has no effect. The same authors found (171) that 40 per cent of neoarsphenamine arsenic was recovered in bile in seventy-two hours. A similar per cent of mapharsen arsenic was



accounted for in the bile in a forty-eight hour period. Most of the arsenic was excreted during the first twenty-four hours following its administration. Choleresis did not increase the biliary excretion of arsenic. No evidence of an enterohepatic circulation was obtained, since bile rich in arsenic when administered to a second biliary fistula dog failed to cause arsenic excretion in the bile of the recipient. Drill *et al.* (172) demonstrated an abnormal liver function, as judged by bromsulfalein retention and phosphatase activity in serum and bile, in fourteen dogs with external biliary fistula one to twelve days after operation. The daily bile volume output of these animals was normal.

Ivy *et al.* (173) found no increase in bilirubin output in the duodenal drainage of normal human subjects within four hours after the introduction of aloes and podophyllum (resin) into the duodenum.

Chloracetylcholine chloride markedly stimulates bile formation in the dog, although the response is somewhat delayed, according to Finnegan & Emerson (174). That this effect is a true cholepoiesis is indicated by the fact that both volume and specific gravity increase, while the color remains unchanged. The choleresis is independent of the transient fall in blood pressure which follows injection of this compound. Chloracetylcholine chloride has a cholepoietic effect similar to that of chloracetate, which it probably liberates in the body. Morrison (175) found that  $\alpha$ -chloropropionic,  $\alpha$ - and  $\beta$ -bromopropionic, and  $\alpha$ -bromobutyric acid, when injected intravenously as the sodium salts, have a hydrocholeretic effect similar to "decholin" except that the response is much more prolonged.

Almquist *et al.* (176) have demonstrated that deproteinized milk contains a heat-stable substance (resistant to boiling at pH 4 to 5) that causes cholic acid production and prevents gizzard erosion in chicks. The cholesterol and estrogens of milk did not prevent gizzard erosion. It would be of interest to know whether or not this fraction of whey would prevent the duodenal ulcer that frequently occurs when bile is excluded from the dog's gut or when chronic liver injury is produced (177). Duodenal ulcer, associated with impaired liver function and protein-deficiency, has been reported by several authors (178 to 181). That the dietary factors concerned in gizzard erosion and in ulcer associated with protein deficiency are different is indicated by the fact that feeding desiccated ox-bile to protein-deficient dogs did not prevent

duodenal ulcer (182). Presumably it would prevent gizzard erosion, since it contained cholic acid.

Bastos & Pinto (183) found a diminution in the vascular bed, interstitial hemorrhage, and thickening of the vessels in the ulcer region of the duodenum in dogs with obstruction of the common bile duct; 80 per cent of the obstructed animals in their series of twenty animals developed ulcer.

Member *et al.* (184) found that the cholesterol content of the blood and aorta of rabbits fed cholesterol was markedly increased by feeding cholic or glycocholic acid with the cholesterol. Dehydrocholic, hyodesoxycholic, and desoxycholic acid did not possess this property. The cholesterol content of the liver was increased by feeding glycocholic acid but not by desoxycholic acid. Cholic acid differed from the other acids tested in that it increased the concentration of combined cholesterol in the blood. These results indicate that the effective bile salts probably increased cholesterol absorption. Li & Freeman (182) found that the fattiness of the liver of protein-deficient dogs was more uniformly high if desiccated ox bile was fed with the diet, owing probably to more uniform fat absorption. Selye (185) demonstrated that the steroid hormones can be absorbed in the absence of bile when administered in large amounts by stomach tube.

Walzer *et al.* (186) demonstrated the characteristics of an allergic reaction involving the passively sensitized gall bladders of rhesus monkeys. The serum of a person sensitized to cotton seed protein was injected into the gall bladder and one week later an extract of this protein was injected intravenously. In one to two minutes the sensitized area of the gall bladder turned gray, then superficial vessels became pronounced, and the wall thickened and became edematous. These results suggest how the gall bladder might react if sensitized, but there still is inadequate information as to whether or not sensitization of the gall bladder actually occurs.

Okey (187) has presented a more detailed account of the experimental production of gall stones rich in pigment and mineral by feeding cholesterol. Guinea pigs fed cholesterol and maintained on a synthetic diet produced gall stones if they received dried grass tips and extra riboflavin in addition to the basic vitamin supplement.

Boyden & Layne (188) have demonstrated that a relatively high incidence of cholelithiasis and cholecystitis occur in patients

with pernicious anemia and suggest that there may be some etiological relation between pernicious anemia and disease of the gall bladder. The increased pigment excretion in pernicious anemia suggests itself as a basis for relating one condition with the other. It would be interesting to know whether or not Okey's guinea pigs with cholelithiasis also had a higher hemolytic index than the guinea pigs without stones. Perhaps the additional supplements permitted more pigment synthesis and destruction to occur in these guinea pigs.

The macrocytic anemia reported by Crandall *et al.* (189) as occurring in bile fistula dogs has been corroborated by Last & Last (190) who find this anemia unsuited for the assay of antipernicious anemia factor. The degree of anemia was too variable and it failed to respond to clinically potent liver extract.

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# KIDNEY<sup>1</sup>

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## THE MEASUREMENT OF DISCRETE RENAL FUNCTIONS

Advances in renal physiology within the past year have come in large part through the experimental application of precise clearance methods for the measurement of glomerular filtration rate, renal blood flow, and tubular secretory and reabsorptive capacities. Such studies have contributed to an understanding of normal renal homeostatic functions, and to an understanding of the altered functions of the kidney under a variety of physiological conditions. Furthermore these clearance methods, yielding quantitative information of fundamental physiological significance, have found increased clinical use, supplementing and in some instances replacing purely empirical tests of renal function in disease.

*Glomerular filtration rate.*—Various simplified procedures for the evaluation of glomerular function, which obviate the difficulties of infusion and quantitative urine collection inherent in clearance methods, have been suggested (1, 2). The method of Newman, Bordley & Winternitz is based upon the determination of the slope of the line relating the plasma mannitol concentration to time, following the intravenous administration of a single large dose of the hexitol. Since mannitol is rapidly distributed throughout the extracellular fluid compartment of the body ( $V_c$ ), is not metabolized in the body, and is excreted in the urine solely by a process of glomerular filtration, the rate of disappearance<sup>2</sup> of mannitol from this fluid compartment ( $S$ ) is proportional to the glomerular filtration rate ( $C$ ); i.e.,  $S = C/V_c$ . The slope of the plasma concentration curve ( $S$ ), readily determined by the repeated withdrawal of blood samples, expresses glomerular filtration in terms of percentage of the extracellular fluid compartment cleared per minute. Newman

<sup>1</sup> Although this review of necessity is selective, it covers in the main the literature published between July 1, 1944 and June 30, 1945. References to investigations published prior to this period have been included if they provide a basis for, or are pertinent to, an understanding of current work.

<sup>2</sup> The logarithm of plasma concentration is a linear function of time.  $S$  is the slope of this line.

*et al.* feel that this is a logical expression of renal function, for the kidneys are fundamentally regulators of the composition and volume of the extracellular fluid. The difficulty with such an expression lies in the fact that any expansion or contraction of the extracellular fluid compartment, no matter what its basic origin, alters apparent renal function. The diagnostic or prognostic value of such a test is obviously limited. The clearance method of Alving & Miller (3) is simple and is certainly a more sound procedure physiologically, although it necessitates the quantitative collection of urine. For infants, in which quantitative urine collection is well nigh impossible, the simplified procedure of Newman is probably justified.

*Renal plasma flow.*—The introduction of the *p*-aminohippurate clearance by Smith and his associates (4, 5) has greatly simplified the measurement of minimum effective renal plasma flow. The analysis of *p*-aminohippurate by the method of Bratton & Marshall (6) is extremely simple and accurate, in contrast to the laborious procedures involved in the analysis of diodrast, the substance previously in vogue for measuring renal plasma flow (7). Additional advantages of *p*-aminohippurate over diodrast are that plasma and urine blanks are negligibly low, *p*-aminohippurate does not penetrate the red cells either *in vitro* or *in vivo*, it is nontoxic, and it is less extensively bound to the plasma proteins than is diodrast.

The validity of the *p*-aminohippurate clearance at low plasma concentrations as a measure of minimum effective renal plasma flow in man has been tested directly by Warren, Brannon & Merrill (8). A ureteral catheter was passed into the antecubital vein, through the right atrium and inferior cava, and into the renal vein. By comparing the concentrations of *p*-aminohippurate in systemic venous blood and renal venous blood, the renal extraction ratio could be determined directly. At plasma concentrations of *p*-aminohippurate of 2.5 mg. per cent or less, the extraction ratio averaged 0.88, a figure which agrees well with previous determinations on the dog (9), in which a ratio of 0.87 was found. It is presumed that the deficit in renal extraction is in large part due to the admixture in the renal vein of blood from nonexcretory supporting tissues.

By utilizing a neoprene injection technique, Shonyo & Mann (10) have shown that the normal circuit of afferent arteriole, glo-

merulus, and efferent arteriole in the normal mammalian and bird kidney is by-passed in three ways: (a) direct continuations of the interlobular arteries join capillaries of the cortex corticis; (b) vessels in the corticomedullary zone by-pass glomeruli and enter the medullary capillaries; (c) direct anastomoses link arteries and veins in the corticomedullary zone. The proportion of the renal blood traversing these direct channels is unknown. Arteriovenous shunts might contribute in very small proportion to incomplete extraction of *p*-aminohippurate.

*Tubular secretory and reabsorptive capacities.*—The maximum tubular secretory capacity ( $T_m$ ) for *p*-aminohippurate will undoubtedly displace that for diodrast as a routine measure of functional tubular excretory mass. The advantages of the former substance, listed above in the discussion of renal plasma flow, apply equally well to the measurement of excretory mass (5).

As a general measure of functional tubular reabsorptive mass, the maximum reabsorptive capacity ( $T_m$ ) for glucose (11) remains as the procedure of choice. The reabsorptive mechanisms for vitamin C (12), phosphate (13, 14), sulfate (15), and certain amino acids (16, 17) are likewise limited in their transport capacity. At least theoretically the reabsorptive capacities for these substances might be used to assess tubular mass, although certain practical considerations such as toxicity, especially of amino acids, would limit their usefulness.

#### INTERACTION BETWEEN TUBULAR SECRETORY AND REABSORPTIVE MECHANISMS

*Specific secretory competition.*—The number of discrete cellular mechanisms concerned with the active transport of materials across the renal tubular epithelium must, on *a priori* grounds, be limited. The number of compounds known to be transferred by such mechanisms increases each year. It is, therefore, not surprising to find that several compounds are handled by a single mechanism, and compete for that mechanism in such a way that the secretion or reabsorption of one compound is depressed by the simultaneous presentation to the kidney of another compound transported by the same mechanism. Thus phenol red, diodrast, hippuran (7), *p*-hydroxyhippuric acid, *p*-aminohippuric acid, *p*-acetylaminohippuric acid (4), *m*-aminohippuric acid, *m*-hydroxyhippuric acid, 2-pyridone-1-acetic acid, cinnamoylglycine (5), and

penicillin (18, 19) are all secreted by a single tubular mechanism, and compete for that secretory mechanism when they are simultaneously presented to the kidney.

The nature of this competition finds ready explanation in a mechanism of tubular secretion proposed by Shannon (20). The tubular cells are presumed to contain a fixed limited amount of some component with which the substance secreted combines. The breakdown of this compound delivers the substance into the tubular lumen. Since the quantity of the cellular component is limited, the secretory mechanism may be saturated by transforming all of the cell component into its combined form. The rate of tubular transport of the material is then solely a function of the rate of breakdown of this complex. If two or more substances combine with a given type of cellular component during secretion, they may mutually displace each other from combination. Hence, when administered together they mutually depress their individual rates of secretion.

*The secretory blockade of penicillin.*—The competition between diodrast or *p*-aminohippurate and penicillin has been turned to practical clinical use to reduce the rate of urinary loss of the latter substance (18 to 25). Beyer and his associates have advocated the simultaneous administration of penicillin and *p*-aminohippurate as a means of effecting a physiological economy of the antibiotic agent, of maintaining its plasma concentration at high levels, and of maintaining a therapeutic concentration in the plasma following a single parenteral dose for a long period of time. *p*-Aminohippurate is nontoxic, and in a pathological sense does not affect renal function, for the depression of penicillin excretion which it causes is completely reversible. Whether the method of Beyer is to find wide clinical application will depend in large part on economic considerations, namely, the relative cost and availability of penicillin and *p*-aminohippurate. Other methods of delaying penicillin excretion, namely, injecting it with epinephrine (26), in peanut oil (27), as an albumin-penicillin complex (28), and cooling the site of injection with ice (29), all suffer from a common failing. They attain economy of the drug by delaying its absorption, thereby reducing its plasma concentration and rate of excretion. Oral administration of penicillin (30, 31, 32) offers a technically more feasible means of maintaining therapeutic levels for long periods of time than does simultaneous parenteral administration of penicillin and *p*-amino-

hippurate. The oral route, however, is highly wasteful, for some five times the intramuscular dose is required *per os*. If relatively crude effective preparations can be produced cheaply, the repeated oral administration of such penicillin may provide the simplest solution to the problem in a majority of instances. Otherwise, secretory blockade of penicillin by *p*-aminohippurate may well come into common clinical use.

*Specific reabsorptive competition.*—Reabsorptive competition between various compounds likewise exists. Thus glucose and xylose (33) compete for a single carbohydrate reabsorptive mechanism. Creatine, glycine, glutamic acid, and presumably other amino acids (16, 17) compete for an amino nitrogen reabsorptive mechanism. Undoubtedly this latter competition accounts in part for the creatinuria observed following the intravenous administration of amino acid digests (34, 35), although increased creatine formation and altered distribution of creatine between tissues and blood may likewise play a role. The basis for this reabsorptive competition, like that for secretory competition, appears to be the presence within the tubular cells of a limited quantity of a cellular component with which the reabsorbed material combines. The cellular components for the carbohydrate mechanism and the amino nitrogen mechanism are distinct, for glucose and glycine do not compete in reabsorption.

*Nonspecific competition.*—A more puzzling type of competition between renal mechanisms has recently been disclosed. Selkurt (36) has shown that the infusion of hypertonic solutions of sodium or potassium chloride temporarily depresses the reabsorption of vitamin C. Diuresis is produced by such procedures, yet increase in urine flow *per se* is no adequate explanation, for a purely osmotic diuresis initiated by the administration of mannitol does not affect reabsorption of vitamin C. Vitamin C is an electrolyte. Perhaps the reabsorptive processes for chloride and vitamin C, like the reabsorptive processes for chloride and bicarbonate, are related in some as yet undisclosed manner. But more difficult of comprehension is the depression of vitamin C reabsorption by saturation of the secretory mechanism for *p*-aminohippurate, and by saturation of the reabsorptive mechanism for glucose (37). Similarly difficult to understand is the observation of Bonsnes, Dill & Dana (38) that the reabsorption of uric acid is depressed by saturation of the secretory mechanism for diodrast. According to Selkurt such compe-

tion is explicable by assuming that the energy available to the kidney for either secretion or reabsorption is limited. Channeling the energy available into one mechanism might reasonably be expected to reduce the energy available to another. Such an explanation might account for the depression of phosphate reabsorption by saturation of the glucose reabsorptive mechanism (14). However, the observation of Selkurt that in the dog the reabsorption of glucose does not affect the secretion of *p*-aminohippurate, would seem to cast considerable doubt on such a simple explanation. Perhaps it is safest to say that there may be several varieties of competition between renal mechanisms and that each requires further elucidation.

*The practical import of competition.*—Whatever may be the explanation of such nonspecific interactions between secretory and reabsorptive mechanisms, the fact of such interaction has a practical bearing upon assessment of renal function in man. According to Klopp, Young & Taylor (39), the simultaneous measurement of maximum tubular reabsorptive capacity for glucose (glucose *Tm*) and minimum effective renal plasma flow (*p*-aminohippurate clearance) yield abnormally low values for plasma flow. Similarly, saturation of the glucose reabsorptive mechanism depresses the maximum secretory capacity for *p*-aminohippurate.<sup>3</sup> These and other interactions which occur between discrete renal mechanisms indicate that the simultaneous measurement of more than one renal tubular function may give erroneous values.

#### FACTORS ALTERING RENAL FUNCTION

*Anesthesia.*—Light ether or light cyclopropane anesthesia does not appreciably alter renal function in dogs (40) or in man (41), nor does light sodium pentobarbital anesthesia exert any significant effect on renal function in the dog (42). However, according to Craig, Visscher & Houck, deep ether or cyclopropane anesthesia (stage III, plane 3) decreases urine flow, glomerular filtration rate, and renal blood flow by approximately one-half. The reduction in blood flow and filtration rate is attributed to neurogenic vasoconstriction of the afferent arterioles. These investigators account for the well known "denervation hyperemia," described in older experiments on deeply anesthetized animals, in terms of release from

<sup>3</sup> Note that the results on man and dog are not in agreement on this point.



the high vasoconstrictor tone which the anesthetic agent produces.

*Ageing.*—In a study of fifteen colored male subjects, ranging in age from 70 to 85 years and without clinical signs or previous history of renal or cardiovascular disease, Shock (43) found glomerular filtration rate and minimum effective renal plasma flow to be reduced by 45 and 60 per cent, respectively, in comparison with generally accepted adult standards. Diodrast *Tm* was reduced by 40 per cent. Accordingly, filtration fraction was elevated above normal, and the kidneys were relatively ischemic, i.e., low diodrast clearance per unit of diodrast *Tm*.

According to MacNider (44), stainable lipid in the proximal convoluted tubules of dogs progressively increases with age. However, in the flattened embryonal proximal cells typical of healed nephritis, no lipid is found, even in senile animals. The storage of lipid is presumed to result from some normal modification of cellular metabolism with ageing, not evident in regenerated epithelium.

Zwemer & Wooton (45), in contrast, find little lipid in the kidneys of fasting guinea pigs. However, following large doses of cod liver oil, fat droplets appear in the glomerular capsule, in the tubular lumen, and in the cells of the proximal and collecting tubules. These authors suggest a normal filtration and tubular reabsorption of fat. To the reviewer, a more reasonable view would be that the appearance of particulate fat in the glomerular filtrate is an indication of imperfection of the glomerular membrane. The quantities of oil administered were far outside of any physiological range.

*Anoxia.*—At a simulated altitude of 25,000 ft., normal rats show polyuria and increased chloride excretion. Subtotal nephrectomy (46) and the administration of quinine or uranium (47) duplicate these effects at sea level. The polyuria of uranium poisoning is apparently maximal, for no increase occurs at 25,000 ft. The subtotally nephrectomized animals and those given quinine respond with a greater polyuria than the controls, when subjected to low barometric pressures. These results are interpreted as showing that anoxia, like other damaging procedures, diminishes the reabsorptive capacity of the tubules for water and chloride.

Human subjects exposed briefly to simulated altitudes of 18,000 ft. likewise show polyuria and an increased rate of excretion of sodium, potassium, and chloride (48). Following exposure, these

elements are retained, so that total twenty-four hour excretion is unchanged. These observations are in agreement with the well accepted facts that hyperventilation results in a diuresis of an alkaline urine (49), and that the sodium and bicarbonate contents of plasma of individuals residing at high altitudes is reduced (50).

In sharp contrast, studies on urine flow in anesthetized operated animals have indicated that progressive oliguresis, rather than diuresis, results from ascent to simulated high altitudes (51), presumably as a result of progressive diminution in renal blood flow. It is claimed that at 12,000 to 16,000 ft. neurogenic vasoconstriction reduces renal blood flow; at 24,000 ft. the liberation of epinephrine adds a humoral vasoconstrictor effect; and at 30,000 ft. bubble formation begins to occlude the renal vessels. Discrepancies such as these (oliguria as opposed to polyuria) emphasize the fact that observations made on operated animals under anesthesia may not necessarily duplicate those made on normal animals.

*Amino acid infusion.*—In dogs the infusion of glycine, in amounts sufficient to raise the plasma concentration to 20 mg. per cent, produces an increase in filtration rate and renal blood flow, and a decrease in filtration fraction (52). These changes result from a fall in total renal vascular resistance which is predominantly localized in the efferent arteriole and post arteriolar vascular bed. Essentially these same changes are produced by feeding a high protein diet. Presumably circulating amino acids relax the smooth muscle of the renal vascular bed directly. It would be interesting to know whether a similar effect would be exerted in the human hypertensive subject with relative renal ischemia. Glycine in the human subject causes an increase in peripheral blood flow (53).

*Exercise.*—Renal plasma flow is uniformly reduced by brief severe exercise, such as running 440 yds. at top speed, and remains depressed for ten to forty minutes thereafter (54). Glomerular filtration rate and urine flow are significantly reduced in only about half of the subjects tested.

*Pregnancy and toxemia.*—In the normal female no change occurs in glomerular filtration rate, renal blood flow, or tubular excretory mass during the course of a normal pregnancy (55). When a specific toxemia develops during the latter trimester of pregnancy, filtration rate falls and renal blood flow rises (56). Following delivery, renal blood flow returns to normal in about half of the cases, and falls to ischemic levels in the remainder, i.e., in those

which develop a persistent hypertension. In six patients with pre-existing hypertension, glomerular filtration rate and maximum secretory capacity for diodrast remained unchanged during pregnancy, but renal blood flow increased slightly (57). None of these patients developed toxemias, and none showed evidence of renal damage as a consequence of the pregnancy. Similar results were observed in two patients with preexisting chronic diffuse glomerulonephritis. Evidently pregnancy exerts a deleterious effect on renal function in patients with preexisting hypertensive or renal disease, only if a specific toxemia, or an acute exacerbation of the nephritis, develops concurrently.

*Unilateral nephrectomy.*—In rats, removal of one kidney leads to hypertrophy of the remaining one. According to Reid (58), a diet high in protein increases the hypertrophy, not as a result of an increased excretory load on the kidney, but as a result of increased availability of essential amino acids needed to increase renal mass.

In the human physiological evidence of hypertrophy of the remaining kidney was obtained in one patient following removal of a functional kidney for bleeding pelvic erosions (59). In another, in which a nonfunctional adenocarcinomatous kidney was removed no evidence of subsequent hypertrophy of the normal kidney was found. However, since this kidney was functionally equivalent to two-thirds of two normal kidneys at the start, it is apparent that maximal hypertrophy had taken place prior to removal of the diseased nonfunctioning organ.

*Sex hormones.*—Selye (60) first demonstrated that testosterone propionate causes marked enlargement of the kidneys of the mouse. Histologically these kidneys are characterized by pronounced hypertrophy of the epithelium of the proximal and distal convoluted tubules, and of the epithelium of the parietal lamina of Bowman's capsule. In a comparison of the renotropic with the androgenic activities of various steroids in the rat, Kochakian (61) observed that renotropic effects are related to chemical structure, not to androgenic activity nor to solubility. A 17- $\alpha$ -hydroxy group is necessary for maximum renotropic effects in the rat. Testosterone propionate increases the alkaline phosphatase content of the kidney (62), and both testosterone propionate and methyl testosterone increase the arginase content (63).

In the dog the repeated administration of testosterone propionate increases the functional capacity of the renal tubules to

secrete diodrast, without altering glomerular filtration rate or renal blood flow (64). However, in man, neither testosterone nor testosterone propionate (90 to 300 mg. per day for eight to twenty-three days) has any effect on filtration rate, renal blood flow, *Tm* diodrast, and *Tm* glucose (65, 66). Similarly, the administration of  $\alpha$ -estradiol benzoate to female patients (4 to 6 mg. per day for nine to twelve days) has no effect on glomerular filtration rate, renal blood flow, *Tm* diodrast, or *Tm* glucose, although *Tm* ascorbic acid is reduced, as previously noted in the dog (67). The authors wisely point out not only that marked species differences are to be expected in the effects of hormones on renal function, but also that individual hormones do not affect all renal functions equally.

Oster (68) has demonstrated in the rat that tissue aldehydes which stain with the Feulgen reagent are characteristically concentrated in the intercorticomedullary zone of the kidney. These tissue aldehydes undergo cyclic changes in concentration, increasing in estrus, decreasing in diestrus.

*Diabetes.*—Glycosuria occurs when the quantity of glucose delivered into the renal tubules in the glomerular filtrate exceeds the capacity of the tubules to reabsorb. The quantity of glucose filtered is a function of both glomerular filtration rate and plasma glucose concentration. In the young diabetic patient both glomerular filtration rate and glucose tubular reabsorptive capacity are within normal limits. Therefore the plasma concentration at which glucose first appears in the urine (renal threshold) is the same as that of the normal individual (69). In the elderly diabetic the renal threshold is commonly elevated, not as a result of any marked alteration in the capacity of the tubules to reabsorb, but because of a characteristic decrease in filtration rate. Only recently has the cause of this pathological depression in filtration rate been appreciated (70, 71). In the elderly diabetic deposits of dense hyaline material are commonly found within the glomeruli between the capillary loops. All or most glomeruli are involved in some degree, a few to the extent of almost complete obliteration. The condition, termed intercapillary glomerulosclerosis, increases in frequency with age in diabetics. It is occasionally seen in senile nondiabetics.

*Shock.*—Lauson, Bradley & Courmand (72) and Richards (73, 74), studying renal function in patients in shock, found that glomerular filtration rate and renal blood flow are reduced about in

proportion to the degree of shock. The decrease in filtration rate and blood flow is much greater than can be explained by the fall in blood pressure, and results from active renal vasoconstriction, mainly of the efferent arterioles. Renal vasoconstriction plays a homeostatic role in shock, for normally one-fourth to one-third of the resting cardiac output perfuses the kidneys. Circulatory homeostasis, however, is effected at the expense of renal function, for oliguria or anuria, and loss or impairment of concentrating power are direct results of decreased circulation through the kidneys. Selkurt (75) maintains that a brief period of renal ischemia causes a prolonged constriction of the renal arterioles and a profound dysfunction of the renal tubules, reflected in a reduced capacity to secrete *p*-aminohippurate. Accordingly he feels that the *p*-aminohippurate clearance must be used with caution as a measure of renal plasma flow in shock, and in other conditions of relative anoxia. A similar view has been expressed previously (76).

As a result of the fall in blood pressure or renal anoxia, renin appears in the blood of animals in shock (77 to 81). In general, animals with intact kidneys are more resistant to procedures which induce shock than are nephrectomized animals. A variety of evidence indicates that the renal pressor mechanism (renin, angiotonin) may play a homeostatic role in the regulation of blood pressure normally, as well as in shock. This view has been questioned recently by Hechter, Bergman & Prinzmetal (82), who claim that renal excretory insufficiency, rather than renin deficiency, accounts for the sensitivity of nephrectomized animals to shock (82).

The renal crush syndrome, i.e., delayed renal failure following crushing injuries to large muscle masses (83), has been variously ascribed to renal anoxia, resulting from prolonged renal ischemia (84), and to the renal toxic effects of methemoglobin (85), myoglobin (86), metamyoglobin (87), and an unidentified labile colloidal constituent of anoxic muscle (88). To produce the complete pathological and physiological picture of the crush syndrome, the several protein substances mentioned above must be injected into animals previously rendered acidotic (85, 86), or into animals whose blood pressure has been reduced to shock levels (87).

In addition to the characteristic degenerative changes in the renal tubules in the crush syndrome, the juxtaglomerular apparatus is enlarged, with increased granularity, hyperplasia, and hyper-

trophy of the afibrillar cells of the media of the preglomerular arterioles (89). It is presumed that these cells have an endocrine function and are responsible for the liberation of a vasopressor substance in shock. The intraperitoneal injection of trypsin produces renal tubular necrosis similar to that seen in the crush syndrome (90).

*Bright's disease.*—In a recent excellent review Bradley (91) has correlated the structural changes seen in chronic Bright's disease with the functional changes revealed by the newer methods of studying renal function. Other reviews encompass the prognostic significance of the several renal function tests (92), and the practical management and therapy of nephritis (93).

Corcoran & Page (94), comparing renal function in patients with terminal glomerulonephritis and terminal malignant hypertension, found glomerular filtration rate and tubular excretory mass lower in nephritics than in hypertensives. Since renal blood flows were of the same order of magnitude, the kidneys in nephritis were relatively hyperemic in terms of flow per unit of tubular excretory mass, whereas they were relatively ischemic in hypertensives. These facts are correlated with the greater degree of glomerular and tubular damage in chronic nephritis, and with the greater degree of arteriolar obstruction in malignant hypertension. Relative renal hyperemia in nephritis (95) and ischemia in hypertension (96) have been observed previously in studies on patients with less severe degrees of renal damage.

The protein content of edema fluid in acute glomerulonephritis has been found to be uniformly low (97), suggesting that its cause is water and salt retention secondary to disturbed renal function, rather than diffuse capillary damage as usually taught.

*Other renal diseases.*—Nation has studied the incidence and significance of a series of congenital renal lesions including agenesis (98), ectopia (99), duplication (100), and aplasia (101), and has pointed out wherever possible distinctive clinical features which permit differential diagnosis during life.

Randall (102) points out that renal lithiasis depends upon renal damage producing a nidus to which the earliest crystal may be attached, and hyperexcretion of certain urinary salts, actually in supersaturation verging on precipitation. Two modes of therapeutic attack upon the latter of these two factors have been outlined by Shorr (103), applicable to the prevention of phosphatic calcium

or magnesium stones. The administration of estrogens, by increasing the excretion of citrate, increases the solubility of urinary calcium. The oral administration of amphogel, by diverting phosphate from urine to feces, reduces the tendency of calcium and magnesium to precipitate in the urine as phosphate complexes.

*Gastrointestinal hemorrhage.*—The azotemia which is associated with gastrointestinal hemorrhage results both from a reduction in renal function brought on by dehydration, contraction of circulating blood volume, and hypotension, and from the digestion and absorption of blood proteins (104, 105). The circulatory factors noted above likewise appear to underlie the azotemia of pyloric obstruction (106).

*Experimental nephropathies.*—A minimal nephrotoxic dose of potassium dichromate causes renal necrosis sharply localized to the first part of the proximal tubule; a minimal dose of bichloride of mercury or uranyl nitrate causes necrosis of the terminal part of the proximal tubule (107). Necrotizing doses of mercury and dichromate diminish renal phosphatase activity, whereas a dose of uranium salt, which produces equivalent necrosis, increases renal phosphatase activity (108). The ligation of the ureter protects the hydronephrotic kidney against necrotizing doses of mercury and uranium, but not of diethylene glycol and tartrate (109). It is suggested that the first two agents require concentration within the renal tubules to cause damage, and the latter two do not. The administration of sodium citrate protects the kidney from uranium poisoning (110).

Hemorrhagic kidneys in the rat produced by a diet deficient in choline is presumed to result from decreased formation of phospholipid (111). Renal alkaline phosphatase is reduced in this condition (112). Scurvy in the guinea pig is likewise accompanied by a decrease in renal phosphatase (113). A dietary deficiency of chloride produces extensive tubular necrosis with fibrous tissue replacement in the rat (114). *dl*-Serine is a nephrotoxic agent in the rat, causing tubular necrosis and a reduction in renal cocarboxylase activity (115).

An emulsion of kidney injected into animals of the same species is not antigenic. When combined with living or killed group A beta-hemolytic streptococci or their toxin, the emulsion becomes strongly antigenic, and renal damage is produced (116). It is suggested that glomerulonephritis in man has its origin in slight toxic damage



to the kidneys at the height of a streptococcal infection. Material from the damaged kidneys plus streptococci or their toxin serve as antigens for the production of kidney antibodies. If these antibodies reach sufficiently high concentrations, they cause glomerulonephritis by their specific reaction with the haptens of the kidney.

#### THE EXCRETION OF WATER AND SALTS

*Antidiuretic hormone.*—It is well recognized that diabetes insipidus results from damage to the supraopticohypophyseal mechanism for secretion of antidiuretic hormone. In the absence of this hormone, and in the presence of some hormonal influence exerted by the anterior lobe of the pituitary, the capacity of the distal segment of the renal tubules to reabsorb water is reduced and polyuria results. In a study of forty-two clinical cases of persistent polyuria, evidence of involvement of the supraopticohypophyseal system was found in thirty-four (117, 118). Since all available cases exhibiting a fluid intake of 6,000 cc. or more per day, and an output of 4,000 cc. were included, the eight cases of unexplained origin probably included some examples of psychogenic polydipsia. Hickey & Hare (119) have proposed a test to distinguish clinically between true diabetes insipidus and psychogenic polydipsia. When hypertonic sodium chloride (2.5 per cent) is administered intravenously to a subject with normal posterior pituitary function, the chloride  $R/P$  ratio<sup>4</sup> falls below 1.0, i.e., the renal tubules conserve water in preference to chloride. This relative conservation of water is dependent upon the liberation of large amounts of pitressin from the pituitary as a result of stimulation of the hypothalamohypophyseal system by the hypertonic solution (120, 121, 122). When the same hypertonic sodium chloride solution is administered to a patient with true diabetes insipidus, the chloride  $R/P$  ratio rises above 1.0, i.e., the renal tubules do not conserve water in preference to chloride, presumably because the pituitary antidiuretic hormone is lack-

<sup>4</sup>  $R$  is the virtual chloride concentration of the tubular reabsorbate, i.e., the concentration which would be attained if the chloride reabsorbed per unit of time were dissolved uniformly in the water reabsorbed per unit of time.  $P$  is the plasma chloride concentration. A chloride  $R/P$  ratio above 1.0 obviously indicates that chloride is being conserved in preference to water; an  $R/P$  ratio below 1.0 indicates that water is being conserved in preference to chloride. These facts are independent of the actual urine flow.

ing. Patients with psychogenic polydipsia, having normal pituitary function, respond as do normal subjects.

According to Sharrer & Sharrer (123), secretory droplets formed in the supraoptic nucleus may be traced along axons of the supraopticohypophyseal tract, and may be seen to enter the pituitary gland. They suggest formation of pitressin in the nucleus, and liberation into the blood stream in the gland. In partial confirmation of this view Hare *et al.* (124, 125, 126) have found by assay appreciable amounts of antidiuretic hormone in the supraoptic nucleus.

Morphine exerts an antidiuretic effect by causing the liberation of pitressin (127). Since physostigmine potentiates the effects of morphine, it is suggested that acetylcholine may be involved in the process of hormone secretion. Nicotine likewise exerts an antidiuretic effect through the liberation of pitressin (128).

As a test of tubular water reabsorptive function, Pasqualini (129) suggests the measurement of urine flow from thirty to ninety minutes after the ingestion of 1 l. of water and the subcutaneous administration of 5 units of pitressin. In normal subjects from 16 to 76 cc. of urine is eliminated in 60 min.; in nephritic patients, more than 80 cc. is eliminated. The substitution of pitressin for the twenty-four hours of fluid deprivation in the Addis concentration test is unsatisfactory (130). Maximum specific gravity after pitressin never reaches that attained after fluid deprivation, and is subject to much wider variations. Pitressin tannate gives evidence of exerting a residual antidiuretic effect in dogs as long as nine days after administration (131).

*Adrenal cortical hormone.*—According to Gaunt and others, the anterior lobe of the pituitary exerts its major diuretic influence through its corticotropic effect (132 to 135). Thus hypophysectomized rats and adrenalectomized rats show a delayed and diminished diuretic response to water, and increased susceptibility to water intoxication, which are relieved by desoxycorticosterone acetate or adrenal cortical extract. The increased diuretic response of hyperthyroid rats is abolished by adrenalectomy. Epinephrine increases the diuretic response of both normal and adrenalectomized rats but does not protect against water intoxication (136, 137).

*Water.*—When water is administered *per os* over long periods of time at rates of 6 to 10 cc. per min., Wolf (138) has shown that

urine output exceeds intake, and dehydration results. This seeming anomaly results from the minimal diuretic excretion of 1.2 mg. of chloride per cc. of urine with consequent depletion of body stores of sodium chloride. Additional water is lost to maintain body chloride concentration approximately constant. Basically these principles have been applied by Schemm (139, 140) in his somewhat heroic, but effective treatment of massive edema. A low salt intake, an acid ash diet, and forced fluids (as much as 15 l. of water in twelve hours), by favoring the loss of salt, have repeatedly cleared edema where other procedures have failed.

Water diuresis in the rat, as in man and dog, results from diminished tubular reabsorption of water (141). Renal blood flow and glomerular filtration rate are stable and unaffected by the ingestion of water. In man work at comfortable room temperatures does not inhibit water diuresis, whereas work under hot humid conditions does, even though fluid lost in sweat is replaced at brief intervals (142). Variable results reported on effects of exercise on urine flow may result in part from these temperature effects and in part from differences in hydration of the subjects (143). Urine pH in water diuresis falls if initially high, rises if initially low (144). Adenosinetriphosphate inhibits water diuresis in man, and its effect is enhanced by the administration of ammonium chloride (145).

Weller (146) has proposed the determination of histochemical changes in the kidney as a method of studying renal physiology. He has calculated that intracellular water constitutes 59 per cent of the weight of the renal tubular cells under conditions of normal hydration. His calculations indicate that these cells swell, not only during water and saline diuresis but also during dehydration. The extreme indirection of the calculations, necessitated by the complexities of the kidney, make the method somewhat less convincing when applied to this organ than when applied to others.

*Diuretics.*—In a controlled series of comparisons on ambulatory clinic patients with congestive heart failure, mercupurin and mercuhydrin were found to be equally effective as diuretics (147). Mercuhydrin, however, is the drug of preference, since its injection is attended with less pain. Mercupurin is a more effective diuretic than sodium dehydrocholate (148). Melamine, adenine sulfate, and formoguanamine are nontoxic and highly potent diuretics in the rat and dog. Diuresis produced by these agents is relatively unaffected by pitressin (149). Even gelatine in saline,

in comparison with saline alone, is a diuretic when administered intravenously to dogs (150).

*Salt.*—Wolf (138, 151) has defined the "threshold of retention" of sodium chloride as that plasma concentration above which sodium chloride is more concentrated in the urine than in the plasma at all rates of urine formation. He maintains that this "threshold of retention" is constant at about 6 mg. of sodium chloride per cc. of plasma, in contrast to the variable and indefinite "threshold of appearance" of sodium chloride in the urine outlined by Hare *et al.* (152). When saline containing less than 6 mg. per cc. is administered, the urine formed is more dilute than the solution given. When stronger saline (more than 6 mg. per cc.) is administered the urine formed is more concentrated. Mere constancy does not appear to justify the use of "threshold of retention" in preference to "threshold of appearance." It is doubtful if Wolf can define the former term more closely than to say that it lies within a range of 5.5 to 6.5 mg. of sodium chloride per cc. One can certainly define a threshold of gross or frank excretion within these same limits. The concept of "threshold of retention," though no doubt valuable in certain instances, tends to obscure the fact that no complete definition of factors controlling the tubular reabsorption of sodium chloride has yet been given. Through an apparent misunderstanding of the data of Hare (152), Barclay & Cooke (153) maintain that the capacity of the renal tubules to reabsorb salt is limited and that an absolute renal threshold of some degree of constancy is definable.

During fasting and fluid deprivation water is lost, at first predominantly from the extracellular phase, and later from the intracellular phase. The rate of water loss is reduced by the ingestion of carbohydrate which spares protein, reduces urinary nitrogen, and yields water of oxidation. When fish is eaten, the extra nitrogen metabolized requires the fluid available in the body water of the fish for excretion (154). No gain in water is obtained. Dry protein in a ration increases dehydration because the extra nitrogen metabolized requires extra water for excretion (155). The ingestion of sea water causes extreme dehydration, especially of the intracellular phase, and death from central nervous system damage rapidly ensues (156).

A syndrome characterized by excessive loss of sodium, chloride, and water, resulting in collapse, and associated with renal disease rather than adrenal disease, has recently been described by

Thorn *et al.* (157). Patients exhibiting this syndrome respond well to high salt and sodium bicarbonate therapy, but not at all to the administration of adrenal cortical hormone. The incapacity of these patients to excrete ammonia and to conserve salt and water, combined with an absence of glycosuria would suggest that distal tubular function is much more severely deranged than proximal tubular and glomerular function. Eventually these patients progress to absolute renal insufficiency and death in uremia.

Inorganic phosphate is reabsorbed from the glomerular filtrate by an active tubular reabsorptive mechanism which is limited in its transfer capacity (13, 14, 158). According to Pitts & Alexander (14) the maximal rate of phosphate reabsorption is unaffected by increasing the renal reabsorptive load of sodium chloride or by the induction of acidosis or alkalosis. Parathyroid hormone does not affect the activity of the phosphate reabsorptive mechanism (159, 160), and the characteristic effects of the hormone on calcium metabolism are independent of the kidneys (161). The subcutaneous administration of citrate to dogs causes an increase in urinary calcium excretion, and if repeated at intervals, causes demineralization of the bones (162).

#### REGULATION OF ACID-BASE BALANCE

One of the major homeostatic functions of the kidney is the regulation of neutrality of the body fluids. Since the usual diet contains a relative excess of the potential acid forming substances, phosphorus and sulfur, the excretion of phosphoric and sulfuric acids without loss of equivalent amounts of fixed base is a prime necessity. The two renal mechanisms which accomplish this end, namely, the mechanism of ammonia secretion and the mechanism of excretion of free titratable acid, have recently been subjected to experimental analysis.

*Ammonia secretion.*—Since Nash & Benedict (163) first demonstrated that urinary ammonia is synthesized by the renal tubular cells from some precursor in the renal arterial blood, the nature of that precursor has excited controversy. Urea nitrogen (164), amide nitrogen (165), and amino nitrogen (166) have been variously suggested as the probable parent substance of urinary ammonia. Recently Van Slyke *et al.* (167) have demonstrated that most of the urinary ammonia is formed in the kidney by the enzymatic cleavage of the amide nitrogen of glutamine. A variable

and less significant fraction of ammonia is derived from amino acid nitrogen. Urea apparently is excreted entirely unchanged, a finding consonant with previously expressed views (168, 169) that it is not the precursor of ammonia.

The identification of glutamine as the precursor of urinary ammonia is based upon the development of a specific enzymatic method (170) and a specific gasometric method (171) for glutamine in plasma. According to Archibald (172) and Hamilton (173), glutamine nitrogen constitutes 18 to 25 per cent of the total free amino acid carboxyl nitrogen of plasma. Its concentration is not appreciably affected by acidosis, alkalosis, or chronic renal disease. Therefore, the plasma glutamine concentration is not the prime factor in determining the rate of urinary excretion of ammonia. What factor or factors are significant remain to be determined.

The kidney contains large amounts of glutaminase (170), *l*-amino acid oxidase (174), and *d*-amino acid oxidase (175). In chronic renal disease in the human, the glutaminase content of the kidney is reduced (170). In experimental hypertension in the dog the amino acid oxidase content of the kidney is reduced (176). The reviewer infers that depletion of renal enzymes concerned with ammonia secretion is a basic factor in the incapacity of the patient with chronic Bright's disease to form adequate amounts of ammonia (177), and hence is one cause of terminal acidosis.

*Excretion of titratable acid.*—According to Pitts & Alexander (178, 179, 180), the renal mechanism for excretion of titratable acid is a quasi-secretory tubular mechanism. Buffer salts delivered to the renal tubules in the glomerular filtrate give up fixed base in exchange for hydrogen ions formed within the renal tubular cells. The fundamental process consists of the exchange of  $\text{Na}^+ \rightleftharpoons \text{H}^+$  across the tubular epithelium and is thus similar to a mechanism of base accumulation in marine algal cells proposed by Brooks (181). The hydrogen ions dissociated within the tubular cells are derived from carbonic acid. Renal carbonic anhydrase plays a role in this process by bringing about the rapid hydration of carbon dioxide to carbonic acid within the tubular cells. Sulfanilamide, which in high concentrations is an effective inhibitor of carbonic anhydrase (182), reduces the capacity of the kidney to excrete titratable acid (179). A number of previous investigations have

indicated that the enzyme plays a role in acidifying the urine (183, 184, 185), although for the most part the experiments have not been conclusive.

At least three factors are known to determine the rate of excretion of titratable acid, namely, the amount of buffer presented to the renal tubules in the glomerular filtrate, the  $pK'$  of the buffer, and the plasma alkali reserve (180). An increase in the quantity of buffer, an increase in  $pK'$  of the buffer (i.e., within the range of  $pK'$  4.0 to  $pK'$  7.4), and a decrease in plasma alkali reserve all serve to increase the rate of excretion of titratable acid. Plasma pH seems to be a minor factor, if indeed a factor at all (160).

Both ammonia secretion and excretion of titratable acid are known to be functions of the distal tubules of the amphibian kidney (186, 187). It is significant, therefore, that in a pathological study of the kidney of a two months old infant who exhibited air hunger and other signs of acidosis since birth, Peterman (188) found necrosis and calcification of the collecting tubules and distal convoluted tubules. Glomeruli and proximal tubules were normal.

#### THE MODE OF EXCRETION OF COMPOUNDS OF CLINICAL AND GENERAL INTEREST

*Sulfonamides.*—The rate of renal tubular reabsorption of the common sulfonamides is greatest for sulfamethazine, and diminishes in order for sulfamerazine, sulfapyridine, sulfadiazine, and sulfathiazole (189, 190). Their rates of reabsorption are essentially linear functions of plasma concentration over a range of 4 to 15 mg. per cent. The administration of sodium bicarbonate or other electrolytes reduces the rate of reabsorption of these drugs (189, 191). The acetylated forms of these compounds are eliminated by filtration and tubular secretion. According to Lehr (192, 193) the solubilities of individual sulfonamides, when present in urine in mixtures, are nearly the same as when they are present alone. Their antibacterial activities in the body are additive. Therefore to attain high antibacterial activity, and yet to avoid renal lithiasis, it is suggested that two or more of the sulfonamides be given, each in half its therapeutic dose.

*Thiourea and thiouracil.*—Thiourea, formerly suggested as a substance for measuring total body water, has been found to be unsatisfactory. When injected, its volume of apparent distribution



steadily increases with time, suggesting storage and destruction (194, 195). The renal clearance of thiourea is roughly the same as that of urea and is accordingly diminished in nephritis. Thiouracil is less rapidly absorbed and excreted than thiourea, and is destroyed in a number of organs, including the kidneys (196).

*Penicillin.*—The nature of the tubular secretory mechanism for penicillin has been treated on page 202. The penicillin clearance at plasma concentrations of 0.05 to 0.41 units per cc. ranges between 755 and 1,120 cc. per min. Since these figures are above the range of normal renal plasma flow, the authors conclude that penicillin causes renal hyperemia (197). In view of the rather inaccurate analytical procedures for penicillin, this conclusion may not necessarily be a valid one.

*Creatinine and creatine.*—When given intravenously, 96 per cent of the administered creatinine is recoverable in the urine in twenty-four hours. When given by mouth, only 50 to 73 per cent can be recovered. It is concluded that creatinine undergoes no transformation in the body and that poor recovery, when given orally, is due to incomplete intestinal absorption (198).

Albanese (199) has shown that variations of 10 to 25 per cent in the daily creatinine excretion occur normally and do not represent errors in collection of twenty-four hour urine samples. It is claimed that creatine excretion normally amounts to about 8 to 10 per cent of creatinine excretion. To obtain this figure Albanese corrects the total creatinine values found by the Folin autoclave method by 10 per cent, which he maintains represents the quantity of preformed creatinine destroyed during heating. It has been previously pointed out that the addition of hydrochloric acid, and its subsequent neutralization in the creatine method introduces a salt error in the Jaffe reaction, depressing the chromogenic power of creatinine solutions. If similar amounts of salt are added to knowns and unknowns, adequate recoveries of creatine and creatinine are possible with hydrolysis in a water bath for three hours (200). The Folin autoclave method is subject to sufficient error to render suspect the conclusion of a normal creatinuria of this magnitude.

*Miscellaneous.*—The clearance of mepacrine is directly related to the excretion of ammonia (201). The clearance of intravenously administered carbonic anhydrase is low, owing to its extensive binding to a nonfilterable plasma colloid (202). The rates of renal

tubular reabsorption of arginine, lysine, and histidine by the kidney parallel their rates of absorption by the gut, and their rates of deamination by the kidney (203).

#### THE RENAL ASPECTS OF HYPERTENSION

*Measurement of blood pressure in experimental animals.*—The standard 4 cm. cuff used in the plethysmographic method of Williams, Grollman & Harrison (204) for measuring blood pressure in the rat has recently been shown to give systolic values some 40 mm. Hg. too low. The cuff found most suitable under all conditions is one 16 mm. in width (205). The common procedure of warming the animal during blood pressure measurement elevates the systolic pressure of normal rats to hypertensive levels (206). In a comparison of Wistar Albino and Wistar Gray Norway rats no differences were found in blood pressure which could be correlated with species or sex. However, blood pressure increased linearly with age over the range of one hundred to nine hundred days (207). A tail plethysmographic method for measuring blood pressure in the dog has recently been described (208).

*Methods for production of experimental hypertension.*—The constriction of the poles and body of the kidneys with ties of thread or umbilical tape leads to the development of a persistent hypertension in the mouse, rat, rabbit, and dog (209, 210). The daily injection of broth cultures of hemolytic streptococci and streptococcus viridans derived from the urine of patients with cardiorenal disease and essential hypertension caused the development of hypertension in 73 per cent of forty-two dogs. Only 20 per cent of the controls developed hypertension (211). Partial occlusion of the renal veins occasionally leads to the development of a mild transitory hypertension. Reoperation and obliteration of the collateral veins which develop increase the effectiveness of the procedure (212).

*Neurogenic versus humoral factors in hypertension.*—Page classifies early clinical cases of hypertension into four categories: (a) simple vasomotor lability, usually on an emotional basis, usually not progressive; (b) prehypertension, similar lability of blood pressure, but progressive; (c) neurogenic hypertension, established hypertension with signs and symptoms of nervous hyperactivity; (d) early essential hypertension, established hypertension on a humoral basis. High spinal anesthesia decreases blood pressure and

increases renal blood flow in neurogenic hypertension, not in humoral hypertension. Perfusion of the isolated rabbit's ear with plasma from cases of humoral hypertension causes vasoconstriction; plasma from cases of neurogenic hypertension has no effect (213). Audiogenic stimulation by an air blast causes an epileptoid seizure in susceptible rats. At first no blood pressure differences exist between these "reactor rats" and their more phlegmatic associates. With repeated stimulation over long periods of time the "reactors" are prone to develop persistent hypertension (214). The authors conclude that their observations provide objective evidence of neurogenic influences in the etiology of hypertension.

The administration of pentobarbital or sympatholytic drugs such as yohimbine and 883 F causes a fall in blood pressure in animals with chronic renal hypertension (215 to 218). According to Reed *et al.* (215, 216) these drugs have no effect in early renal hypertension. Accordingly they conclude that in early renal hypertension the blood pressure is elevated through the operation of a humoral renal pressor mechanism, which is uninfluenced by sympatholytic drugs. In late renal hypertension blood pressure is elevated by a sympathetic neural pressor mechanism which may be blocked by sympatholytic drugs. In animals with neurogenic hypertension produced by section of the buffer nerves, intravenous angiotonin exerts its usual pressor effects. Thus neurogenic vasoconstriction is not sufficiently great to interfere with further constriction by renal humoral pressor substances (219).

Dexter, Haynes, and their associates have made a study of the renal humoral pressor mechanism in man (220). Constriction of the renal artery for 12 minutes caused an increase in the renin content of renal venous blood, but no change in the hypertensinase or hypertensinogen content of blood, and no change in blood pressure (221). Brief compression of the renal artery in dogs likewise did not alter blood pressure significantly. In clinical cases of uncomplicated hypertension, plasma hypertensinogen, hypertensin, and hypertensinase were found to lie within normal limits (222, 223). In liver disease plasma hypertensinogen was low.

Plasma withdrawn from animals during the perfusion of renin is devoid of any vasoconstrictor properties if care is taken to prevent the formation of artifact substances in shed blood (224). It is concluded that angiotonin is rapidly removed from circulating blood, probably by combination with vascular smooth muscle.

Thus assay methods fail to demonstrate it in plasma of hypertensive patients,<sup>5</sup> not because of their gross insensitivity, but because it has been removed in the peripheral circulation. If this view were correct, one might expect to find angiotonin in arterial blood but not in venous blood.

Raska (176) has shown in experimental renal hypertension that there is a decrease in the activity of certain oxidative enzymes which normally destroy humoral pressor substances. He concludes that this diminution in enzyme activity may be a factor in the etiology of human hypertensive disease. Thus diminished aminoxidase activity might permit the accumulation of pressor amines such as tyramine in concentrations sufficient to cause hypertension (225). Oster & Sorkin (226) claim that dihydroxyphenylalanine, which is transformed to tyramine in the body, causes a greater rise in blood pressure in hypertensive animals and men than in normal controls. This fact is disputed by Page & Reed (227). Angiotonin is destroyed not only by processes of anerobic proteolytic cleavage, but also by oxidative processes involving oxidized cytochrome (228). The concentration of cytochrome-*c* is reduced, and the activity of the cytochrome oxidase mechanism is impaired in the kidney in experimental hypertension (176). Likewise the capacity of hypertensive rats to oxidize hydroquinones to quinones is diminished (229). Nonfermentable reducing substances are increased in the plasma in hypertensive disease in man (230).

*Experiments on the chemical nature of renin and angiotonin.*—Angiotonin may be partially purified by repeated precipitation of the active material with silver and mercury salts and with nitranilic acid (231), or by the adsorption of impurities on ionic exchange resins (232). Such preparations, although far from pure, are mixtures chiefly of tetra-, penta-, and hexapeptides. At 0°C. the reaction between renin and renin substrate to form angiotonin proceeds slowly, but the destruction of angiotonin by angiotonase is completely inhibited. Hence in assaying renin substrate, incubation with renin at 0°C. for two hours is recommended (233). The usual preparations of renin are crude mixtures of proteolytic enzymes containing carboxypeptidase, pepsinase, trypsinase, and aminopeptidase. Neither carboxypeptidase nor pepsinase accounts for the renin activity of the mixture (234). Carboxypeptidase can

<sup>5</sup> The methods of Page for demonstrating pressor substances in the blood of cases of "humoral hypertension" (213) are presumed by Landis to be subject to error.

be removed by prolonged dialysis without loss of renin activity. Pepsinase and renin are known to be heterospecific enzymes, since the ratios of their proteolytic activities on  $\alpha_2$ -globulin and carbo-benzoxyl-L-glutamyl-L-tyrosine are widely different. Furthermore pepsitensin and angiotonin, the products respectively of the action of pepsin and renin on plasma, are chemically different substances (235).

*The relation of renal disease to hypertension in the human.*—Surgical conditions of the urinary tract as a general group are not causally related to elevation of blood pressure (236). However, in selected individual cases a definite causal relationship has been demonstrated, and the blood pressure restored to normal by the removal of the offending kidney (237 to 241). In general nephrectomy should be performed in hypertension only if it is the treatment of choice irrespective of the hypertension (242). In bilateral renal diseases such as glomerulonephritis, polycystic kidney, and bilateral pyelonephritis, the kidneys are apparently the cause of the rise in blood pressure; whereas in essential hypertension, the kidney is "the victim of the hypertensive disease rather than the culprit" (243).

*Therapy of hypertension.*—The efficacy of nitroglycerine, sodium nitrite, erythrol tetranitrate, and mannitol hexanitrate in lowering blood pressure in hypertensive patients varies greatly with different individuals. Since a given patient may respond better to one drug than another, the most satisfactory therapeutic agent can be determined only by trial of all (244). In the use of thiocyanate the dose must be individualized for each patient on the basis of blood concentration attained, toxic manifestations, and therapeutic response (245). The hypotensive effects of substances causing inflammatory reactions are due neither to fever nor to leukocytosis (246).

Interest in the experimental therapy of renal hypertension in animals centers chiefly in the parenteral use of renal extracts to increase the antirenin titre of the blood (247, 248, 249), and in the oral use of various oxidized marine oils which exert a hypotensive effect (250, 251).

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## BLOOD COAGULATION, THROMBOSIS, AND HEMORRHAGIC DISORDERS\*

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*Reviews.*—Human plasma protein fractions and clotting agents are reviewed by Cohn *et al.* (42, 43, 44). A new publication on protein chemistry has a chapter on structure of proteins, including fibrin (286), and another on lipoproteins (34). Basic facts of blood coagulation (96, 97), certain factors (120, 353), and theories (95, 357) are reviewed. The growing importance of consideration of enzyme factors in clotting and related processes suggests reference to "immuno-catalysis" (298), bacterial proteinases (215), prostatic enzymes (144), and animal venoms (79). Link's reviews (193, 194) on dicumarol, etc., are authoritative and timely, as is that by Quick (263). Selected clinical reviews deal with the blood (21), vascular diseases, including thrombosis and embolism (64, 343), hemorrhagic diseases (207), hemophilia (162), and vitamin P (179). Older volumes of the *Annual Review of Physiology* are used for text references (93, 156, 262, 307).

*Techniques.*—For simple clotting time (CT), the Lee-White (181) method on venous whole blood continues as first choice, especially clinically (207), but a new attempt has been made to standardize a finger-prick capillary tube method (173), and dilution is recommended to increase sensitivity (47). Modified clotting tests are designed chiefly to evaluate the prothrombin factor, especially in relation to hemorrhagic tendencies, treatment with vitamins K, and more recently also thrombotic conditions and anticoagulant therapy. Whole blood ("bedside") methods (307) are less highly regarded than plasma prothrombin-clotting-time (PCT) techniques, of which the Quick test (258, 259, 263, 266), or modifications (211), is now established as a clinical routine despite continued criticisms as to method and interpretations. The chief interpretative question concerns possible interference by inhibitors (17, 20, 137, 214) and factors other than prothrombin (154, 307), rarely lack of fibrinogen (324). The major technical problem is standardization of test conditions, especially the thromboplastin,

\* This review covers the period from June 1943 to June 1945.

e.g., Hurn *et al.* (146) and others (29, 234), but also the calcium (85, 154, 170), pH, salts, etc. (200). The use of diluted (1:8) plasma definitely increases the sensitivity and specificity of the PCT test (193, 299). In addition to commercially available thromboplastins (307), Russell viper venom is still being studied (170). The two-stage (Iowa) method (307) is particularly valuable for control of prothrombin purification (200, 294) and the Iowa thrombin unit (15 sec. clotting of fibrinogen under standard assay conditions) is the best potency test (307).

## THE CLOTTING PROCESS

### NATURE, PROPERTIES, AND USES OF FIBRIN CLOT

The kinetics of clotting reactions obey definite laws which give significance to such concepts as enzymatic processes, autocatalysis, adsorption phenomena, etc., applicable to the participation of individual factors in the coagulation mechanism (115, 175, 185). The true nature of the fibrinogen-fibrin transformation is not yet elucidated but provocative suggestions are advanced by several recent workers (116, 175, 202, 242, 273). Physicochemical studies (44, 286) indicate no fundamental difference in molecular pattern, but clotting involves a linkage of the elongated attenuated fibrinogen molecules into much larger aggregates, namely, the microscopic (dark-field) quasicrystalline needles and threads, in which the electron microscope reveals filamentous submicroscopic units and the x-rays a "fibrous" structure. According to precipitin tests, the antigenic nucleus of fibrinogen is not altered by denaturation or fibrin formation (275). The processing of human fibrin products (77) especially yields (a) "fibrin foam" (14, 19, 363), an absorbable tampon, and (b) "fibrin films" (14, 101), semielastic protective coverings and dural substitute (148); both are useful vehicles for hemostatic application of thrombin. Clots may be made *in situ* by adding thrombin to fibrinogen solution or plasma. Practical problems of preparing such clots to withstand tension (e.g., in "coagulum suture" of nerves, wounds, etc.) require study of relative tensile strength (RTS), which depends on cross-sectional area, temperature, solidity (water-content), etc. (302, 348). Effects of coagulants and anticoagulants extend over a time period (unrelated to clotting-time) and modify mechanical structure and retraction (syneresis) of clots. Some clot-retraction is favorable to RTS, but definite fibrinolysis is weakening (326).



## FIBRINOGEN

The electrophoretic identification of fibrinogen as a specific plasma protein fraction (distinct from the serum globulins), its isolation (e.g., fractional precipitation by 10 to 15 per cent ethanol, in the cold), purification, and lyophile-drying to a stable, powdery, spongy product are described in the cited reviews (44, 67, 96). Physicochemical data include solubilities, isoelectric point (salt-free) at pH 5.4, molecular shape (filamentous), and size (mol. wt. of 500,000). The molecular type explains anomalies of viscosity, streaming double refraction, etc. Of the older salting-out methods for fractionation, Jaques (153) recommends an equal volume of 2 *M* phosphate buffer mixture (pH 6.6), to avoid denaturation and contamination with heparin-complement. Such fibrinogen solutions reduce hydrogen peroxide and iodine. Denaturation does not alter these reducing powers but conversion to fibrin increases them. Lyons (202), working with materials that may be open to technical criticism [cf. Nolf (243)], alleges: "clotting of fibrinogen by thrombin occurs in at least two stages; the initial step is the liberation of blocked thiol groups in fibrinogen brought about by one component of thrombin; the second, an oxidation, probably by a naphthoquinone complex in thrombin converting protein-SH to protein-S-S-protein (fibrin)." Reduction of -S-S- to -SH groups in early stages of fibrin formation is also suggested by E. M. F. changes (345). The thrombin-fibrinogen interaction is accelerated by phenolic substances having reversibly oxidizable hydroxyl groups, but other reducing agents, although able to convert the thrombin -S-S- groups to inactive -SH forms, are inhibitory because they are unable to complete the cycle by accepting hydrogen from the fibrinogen (116).

Fibrinogen, preferred to fibrin in bioassay of tryptases (96), is digested by trypsin equally well in the native or denatured state (128). The difficult purification of fibrinogen from contaminating plasma proteases may not be essential for certain fibrinolytic studies (39) but is important in evaluating clotting and other properties (95). Besides serving as precursor of fibrin clot, plasma fibrinogen has functions relating to the viscosity of the blood and to the erythrocyte sedimentation rate (224, 364). The last is used practically to speed up erythrocyte sedimentation, e.g., in hematocrit determinations (121). The function of the liver in producing fibrinogen explains rises or falls in the plasma fibrinogen level as

this liver function is stimulated or depressed (104, 150), often in sequence, in a large number of abnormal conditions: (a) dicumarol, which is hypoprothrombinemic, can also reduce the fibrinogen level, usually after a slight increase (150); (b) atabrine elevates the fibrinogen in rats even when liver necrosis is induced (305); (c) methylxanthines (caffeine alkaloids) raise the fibrinogen level even after chloroform poisoning (104), whereas heavy metals cause a rise followed by a fall (105); (d) plasma fibrinogen varies with the blood pressure level (58); (e) a factor from sterile abscesses increases plasma fibrinogen (136); and (f) a slight increase often occurs in experimental scurvy (212, 319) as one of the clotting-system disturbances [cf. hypoprothrombinemia and hypersensitivity to dicumarol (193) and antithrombin increase (212)] which suggests a role in the avitaminosis-C of disturbed liver function (192), apart from the hemorrhagic tendency associated with capillary dysfunction. Disturbed liver function can also affect the fate of fibrinogen indirectly, both by lack of prothrombin (to yield thrombin to clot it) and by upsetting the plasma protease system, with resulting fibrinolysis and other altered properties in certain liver disorders (327, 355). Fibrinogen disappears from stored liquid plasma (172, 328).

Afibrinogenemia, or lowering of fibrinogen sufficient to cause bleeding, is very rare (3), some cases being functional (idiopathic) or even familial (260).

Apart from the preparation of fibrin products, lyophilized human fibrinogen, in freshly reconstituted solution and mixed with thrombin solution immediately before use, has important clinical uses for (a) hemostasis (14, 19); (b) "clot-suture" of wounds (366), ruptured viscera (283), and nerves (306, 326); (c) surface treatment of burns (129, 233); (d) "coagulum-contact" adhesion of skin grafts (50, 329); (e) reconstruction surgery (225); and (f) "coagulum-pyelolithotomy," in surgical removal of kidney stones (57). In some techniques (282, 326, 365), plasma takes the place of fibrinogen solution and a thromboplastic preparation may be used instead of thrombin, provided that adequate prothrombin is present.

#### THROMBIN

Active thrombin is easier to prepare than its precursor prothrombin (77) but the purest products to date (290, 296) do not quite satisfy solubility and electrophoretic criteria, although po-

tencies of two fractions (A. 10,086, B. 13,365) average 11,492 Iowa units per mg. of protein nitrogen. Sufficient consideration must be given to physiologically significant impurities such as (a) thrombin activators (see calcium, phospholipids, "thromboplastin"), (b) thrombinolytic enzymes (see serum tryptase and its precursor tryptogen), (c) clot-inhibitors (see heparin-complement, anti-thrombin). Stability is best assured by freedom from protease and by lyophile-drying (77) but 75 per cent glycerol or 66 per cent sucrose are good preservatives (291). Besides human thrombin (available to the Armed Forces), beef (296) and rabbit (248, 249) thrombins (pseudoglobulins) are now commercially available. Within the past half-decade, as noted in these reviews (93, 262, 307), thrombin has been identified as an enzyme-like (nonproteolytic) plasma protein fraction, with characteristic mode of action and physicochemical properties, e.g., isoelectric point at pH 4.4; soluble in 0.45 per cent saturated ammonium sulfate (cf. prothrombin).

The thrombin-fibrinogen interaction has been studied in relation to clotting-time variations with altering concentrations of (a) thrombin (which obeys "the inverse law") and (b) fibrinogen (which produces minor effects). Numerous modifying influences, mostly nonspecific, e.g., salts, colloids, but some relatively specific (see antithrombin), may be classed respectively as "fibrinoplastic" (clot-aiding) or "antithrombic" (clot-inhibiting) in terms applicable to the second phase of clotting (97). Adsorption phenomena are given prominence under antithrombin (see metathrombin) and in the removal of some thrombin on the fibrin clot (297). Nolf's claim (243) that serum "autolyzed" with chloroform first loses and then regains thrombic potency as the fibrinolytic titer waxes and wanes needs careful confirmation. It could be that some thrombin protected from the initial lysis by adsorption onto serum proteins is eventually released in later stages of a weakening tryptic digestion.

The coagulant action of thrombin has been put to extensive clinical use. It is always applied topically, never by injection. Effective hemostasis is often secured by the solution alone, applied directly, as a spray, or soaked on gauze, etc. As noted above, "fibrin foam" and "fibrin film" freshly steeped in sterile thrombin solution are specially useful because they add the factors of tampon pressure, support, and protective covering. Human products can

safely be sewn up in a wound, with added sulfonamide or other antibacterial agents, if desired. An alternative vehicle of promise (190) is the semidenatured gelatine, "gelfoam" (48). Others on trial are (a) a starch sponge preparation (22) and (b) oxidized (absorbable) cellulose or "soluble cotton" (49, 112, 257, 341), but this may impair the effectiveness of the thrombin (293). Robbins' studies (274) indicate some immunological species differences which strengthen the preference for human products, unless the potency is such that very little of the foreign (thrombin) protein is used.

#### PROTHROMBIN

Electrophoretic data, constant solubility in 37 per cent saturated ammonium sulfate, and uniform activity (1500 Iowa units per mg.) indicate the high purity of a recently reported beef prothrombin (200, 294, 295). It is antithrombin-free and said to be a glycoprotein (4.3 per cent carbohydrate). The isoelectric point is at pH 4.8 (cf. thrombin), and heparin, at pH 7.0, does not alter the electrophoretic mobility. Normal plasma (300 thrombin units per cc.) is computed to contain about 20 mg. prothrombin per 100 cc. The usefulness of reprecipitation by ammonium sulfate (228) is confirmed. Dry prothrombin preparations are stable up to 50° C. and are not denatured (291). Three groups of workers (15, 193, 200) fail to substantiate Quick's suggestion (261, 262) that prothrombin is made up of two components (A and B), although the original experiments are confirmed (246). Activation of prothrombin to thrombin is not achieved by calcium salts alone but requires a thromboplastic agent in addition (200). Species differences refer to immunological properties of prothrombin preparations (274), but there are difficulties (85) in evaluating physiological differences merely on the basis of the PCT test. The instability of prothrombin (and other clotting factors) in preserved liquid and frozen plasma is confirmed (15, 328); compare this with the preservation of prothrombin in lyophilized plasma (164). Nolf's data (243) show that calcium triphosphate does more than merely remove the plasma prothrombin.

*Hypoprothrombinemia.*—Prolonged PCT, as detected by the Quick test or similar methods, continues to attract a great deal of attention, both clinically and in animal experiments. The story of the plasma prothrombin centers around the ability of the liver to

maintain the small but highly essential blood levels of this plasma protein. Liver function must be adequate and there must be enough vitamin K. Among agents inhibiting the liver production of prothrombin, dicumarol and the salicylates are all but specific. The ability to maintain a normal prothrombin level and, particularly to recover from hypoprothrombinemia on administration of vitamin K, together constitute a liver function test which is further evaluated by recent workers (2, 70, 301). The consensus is that the degree of hypoprothrombinemia shows poor correlation with other liver function tests and that the liver damage must be very extensive for failure of response to vitamin K. Association of hypoprothrombinemia with jaundice points to co-existent liver damage and hence suggests an hepatogenous origin of the icterus (314). Hypoprothrombinemia is obtainable experimentally by liver damage with many hepatotoxic agents, e.g., chloroform (104), arsenicals (159) mercurials and other heavy metals (105), quinine (253) and other alkaloidal poisons (277), and toxic sterols related to vitamin A (189). If the liver damage is not too severe, a favorable response is usually obtained with vitamins K and sometimes with methylxanthines (192), and the same is true for the antiprothrombinemic effects of dicumarol, salicylates, indandione derivatives, and aldehydes. Cirrhotic changes (137), extensive liver tumors, e.g., rat tumors (103), and infiltrations, e.g., rat leukemias (318) may also produce hypoprothrombinemia. Emotional shock is said to inhibit the hepatic formation of prothrombin (280).

*Hyperprothrombinemia.*—As a result of improved PCT tests it has recently become evident that plasma prothrombin levels may rise above normal limits, with possible significance in relation to (a) thrombotic tendencies, and (b) modes of action of vitamins K and of methylxanthines particularly in combating hypoprothrombinemia (106, 107, 300, 346, 347).

*Miscellaneous clinical PCT variations.*—Plasma prothrombin studies include repeated attempts, largely futile, to correlate with incidence of hemorrhage in tuberculosis (325) and with severity e.g., as to liver damage, in such infections as syphilis and malaria (66).

*Clot-inhibitors and the prothrombin test.*—Additional data, accumulating in support of the view of Ferguson & Glazko (99) that inhibitors may not be fully controlled in PCT tests, are suggested by Honorato *et al.* in studies of liver cirrhosis (137), of chick

avitaminosis-K (138), and of rats on choline-free diets (139). In peptone shock, the antithrombic factors are increased and prolong PCT (17, 18). Heparin, by interfering with the coagulation processes proper, *in vitro* as well as *in vivo*, may complicate the performance of "prothrombin" tests (20) but Lam (177) finds normal values (in the Quick test) in bloods rendered incoagulable by the intravenous administration of heparin. The "heparin tolerance test" will be reviewed under thromboplastic factors.

### VITAMINS K

Physiological interest in the chemistry of the various natural and synthetic naphthoquinones and related compounds having antihemorrhagic (vitamin K) activity is restricted to facts bearing upon potency, absorption, and other matters concerned with effective administration, and views as to modes of action. It is generally agreed [but cf. Lyons (202)] that vitamin K is not a clotting factor, but a link in certain chemical processes of liver metabolism that result in prothrombin production. It is of theoretical as well as practical significance that, contrary to earlier findings, vitamins K do antagonize the antiprothrombinemic dicumarols, salicylates, etc. (193, 300). Significant chemical interrelationships between naphthoquinones and coumarins find physiological expression in new facts, viz., (a) phthiocol can be converted into 3,3'-methylenebis (2-hydroxy-1,4-naphthoquinone) which has antiprothrombinemic properties (223) and (b) conversely, 3-methyl-4-hydroxycoumarin has some vitamin K activity (222). Taken with the usual lack of liver lesions in avitaminosis-K (78), a reasonable conclusion (263, 360) is that active coumarins, etc., are "anti-vitamins," blocking some metabolic intermediary of prothrombin by the chemically similar but physiologically inadequate coumarin derivative. Caution in accepting this view, however, is indicated by recent evidence that hyperprothrombinemia occurs in normal animals given excess of vitamin K, by what appears to be a liver-stimulating action (13, 107). There is a further suggestion that vitamin K activity is somehow tied up with the metabolism of choline compounds (137, 138, 139). Menadione decreases acetylcholine synthesis in tissue slices (337) and seems not to inhibit cholinesterase but is more likely to act on -SH groups and oxidation-reduction systems (202) [cf. effects on aerobic glycolysis (320) and bacterial enzymes (6)].

In the body nonquinone forms are converted into free quinones (e.g. menadione) and excreted in combination (272). The Russian idea (303) as to phthalates is denied once more on the basis of failure to cure in avitaminosis K experiments (27), but the ability of phthalates to antagonize dicumarol is confirmed (155). Another argument is that indandione derivatives, chemically related to phthalic acid, have the actions not of vitamin K, but of the antiprothrombinemic agents (157).

*Clinical uses.*—Vitamin K is becoming increasingly useful clinically (187). There is continued confirmation of the prophylactic and curative value of vitamins K in hemorrhagic disorders associated with hypoprothrombinemia, e.g., obstructive and other liver-affecting jaundice (254, 314), nonicteric liver disorders (301), hemorrhage of the newborn (358), and other (chiefly experimental) vitamin K deficiencies (156, 226). The major new contribution is that massive doses of K-vitamins can stimulate the liver [cf. methylxanthines (106)] normally (107), in hepatic disorders (301), and in dicumarol (31, 193, 203) and salicylate (192) poisoning. Vitamin K may be of value in the treatment of metrorrhagia (149) and threatened abortions (168); also for menorrhagia (126) and post-partum bleeding (194). Taken in conjunction with the above-mentioned evidence of a liver-stimulating action, these data suggest blood disturbances of liver origin, not only pathologically, but in relation to certain physiological periods of womanhood (126). Vitamin K is of value in hepatitis caused by yellow fever vaccine (338) and it is rational (see above) to "fortify" donor's blood (used in transfusion of such cases) with prothrombin by prior administration of menadione (169). Expectation of therapeutic benefits from vitamins K requires appraisal of the necessary reserve of liver function. This may be inadequate not only in extensive liver damage (301) but also in rare functional cases (idiopathic hypoprothrombinemia) (240). Unlike the chick (52, 53), man and most mammals get adequate K-vitamins from the intestinal bacteria, with food sources playing a secondary role. Deficiency conditions, apart from liver utilization, therefore, are rare, but may at times be associated with failure of absorption, e.g., biliary insufficiency (16), pathological conditions (260), and evacuant removal of fat-soluble vitamins by mineral oil (4). Inhibition of vitamin K production by sulfonamide drugs acting on the intestinal bacteria (171) is antibiotic, not chemical neutralization, since K-activity is retained



after diazo-union between menadione and the sulfonamides (82).

#### ANTIPROTHROMBINEMIC AGENTS

Dicumarol (dicoumarin), or 3,3'-methylenebis (4-hydroxycoumarin) is the most important of these agents and Link (192) reviews this field from the original identification as the toxic agent responsible for the hemorrhagic sweet clover disease of cattle. Other similar compounds studied to date have weaker actions but Fantl's study of 3,3'-ethylidenebis-(4-hydroxycoumarin) leads him to suggest that it might break down in the body to simpler metabolic intermediates of an aldehyde nature (84). Salicylates, especially acetylsalicylic acid, act similarly, though twenty times weaker (7, 193). In view of the enormous medicinal consumption of salicylates and the pertinent literature unearthed by Link, it is remarkable that so little clinical attention has been given to the undoubted hemorrhagic possibilities. That salicylates are physiological intermediates in dicumarol actions is urged by Link because of the ease of chemical synthesis and degradation via salicylic acid and because of the disappearance (not by excretion) of coumarins in the body, but Lester (186) objects on grounds of failure to find salicylates in the urine after dicumarol administration to rats. We have already reviewed the chemical relationships and physiological differences between the coumarins and naphthoquinones and again mention Kabat's finding (157) that indandione derivatives (cf. phthalates) are hypoprothrombinemic agents and not like the naphthoquinones.

*Modes of action.*—Dicumarol is not a true anticoagulant, except for minor *in vitro* inhibitory effects reported by some observers (71). *In vivo*, it lowers the plasma prothrombin and may alter the calcium optimum for the PCT test (154). Its occasional effects on the fibrinogen (150) do indicate that it can act on the liver in other ways and this is confirmed by the finding of a central necrosis of the liver in some animal experiments (192). Nevertheless, for all clinical and other practical purposes, the hypoprothrombinemic action is specific and the chief danger from overdosage is hemorrhage (204, 304). Treatment usually calls for drug withdrawal and blood transfusions but intensive vitamin K therapy is an important adjunct (see above), with due regard for the potential toxicity of high doses of naphthoquinones (271).

Pregnancy and lactation increase the maternal susceptibility to

dicumarol (or acetylsalicylic acid) and lessen the effectiveness of vitamin K, but the sucklings are sensitive to milk-transmitted effects of both drugs (102, 265). In practice, therefore, a mother receiving dicumarol, e.g., for puerperal thrombosis (55), should not be nursing her infant or the latter should receive supplemental vitamin K. Avitaminosis C (scurvy) also increases susceptibility to hypoprothrombinemia (192).

*Treatment of thromboembolic conditions with dicumarol.*—This use of dicumarol is closely related to that of heparin (68, 80, 276). The rational use of dicumarol in prevention and palliation of thromboembolic conditions finds support in physiological evidence that thrombosis is often associated with hypercoagulability (e.g., hyperprothrombinemia), on the one hand, and with increased platelet-adhesiveness (313), on the other. Dicumarol counteracts both mechanisms and its clinical usefulness is receiving widespread confirmation. No attempt will be made to review this clinical literature, nor is it appropriate here to evaluate the place of dicumarol in individual types of intravascular clotting anomalies or amongst other remedial measures. It is relevant, however, to note that coincidental circumstances, e.g., infection, trauma, circulatory stasis (236), are highly important in modifying the success in application of the physiological principles here discussed. The oral method of administration is advantageous but rather slow. It is repeatedly emphasized that a sensitive PCT test be run daily and that great care be exercised since "tampering with the coagulability of the blood, that protective mechanism of life *par excellence*, is in principle a hazardous business" (193).

#### CLOT-AIDING FACTORS

*"Wettable" surfaces.*—The long-known fact that coagulation is quicker in wettable glass, etc. than in non-wettable paraffined or plastic tubes, is put to practical use during blood transfusions, e.g., flexible plastic tubing (367) and war use of discardable cellulose tubing (and nylon filters). Tocantins quantitates clotting-time-differences between glass and nonwettable tubes in testing "anticephalin activity" (which see). Ferguson (96) stresses surface (colloidal) adsorption in activation of plasma (serum) trypsin.

*Calcium salts, etc.*—Ionized calcium salts are ordinarily essential for blood clotting. They activate prothrombin to thrombin in conjunction with thromboplastic factors (295) and act catalyti-

cally (200), cf. Ferguson's "intermediary" complex (90a, 95). Strontium, experimentally, is a weaker and less adequate substitute (200, 270). Since there are optimal salt concentrations above which both first and second phase clotting reactions are inhibited, questions arise as to cation antagonisms (122). The calcium-optimum in PCT tests may be altered after dicumarol (154), but is less significant with use of snake venoms (170), cf. trypsin (97). The still debatable question of protein-bound calcium comes up in connection with oxalation of a coagulant-active "euglobulin" (356).

*Decalcifying anticoagulants.*—Citrate is outstanding among the older decalcifying anticoagulants because they are well tolerated *in vivo*, but danger of toxicity must be kept in mind when giving massive transfusions (1). A new decalcifying mechanism is that of certain ion-exchange resins, e.g., amberlite (315).

*Thromboplastic factors.*—Besides calcium, at least three types of agent, phospholipids, lipoproteins, and proteases, can participate in conversion of prothrombin to thrombin. Hence uncertainty prevails as to the fundamental significance of current data which fail to specify the type of thromboplastic agent, e.g., (a) attempts to promulgate plasma "thromboplastin" or "heparin-tolerance" tests for use especially in connection with anticoagulant therapy (61, 350); (b) evidence for a "thromboplastic" defect (hemophilia-like) in the female (208); (c) assertion that "thrombokinase" is absent from the exudative fluid in burn cases (45); (d) alleged "thromboplastic" action (216) to account for recent findings that digitalis can shorten clotting-time (8, 65, 352), which several deny (237, 312); and (e) Nolf's peculiar views and divergent definition of "thromboplastic" as applied to the activation of "thrombozyme" (243, 244). From more orthodox viewpoints, his data are best interpreted as having to do with the activation of serum trypsinase. (1) *Phospholipids.*—Chargaff (35) and Ferguson (96) reaffirm the thromboplastic activity of cephalin, in tests with a phosphatidyl ethanolamine isolated from brain by Folch (110, 111). Cephalin impurities<sup>1</sup> could explain the finding of some activity in other brain phosphatides, as in early pioneering experiments with commercial (147) and other "lecithins." Nevertheless, the exact identification of natural clot-aiding factors is still incomplete (34), as witness recent confirmation (109) of thromboplastic activity in an uni-

<sup>1</sup> Folch, J., Personal communication.

identified alcohol-soluble lipid from (a) lung lipoprotein (36); (b) Laki's "plasmakinin" (176). The possibility that current tests fail to distinguish between true prothrombin activation and a kinase effect on thromboplastic enzyme precursor (tryptogen) contaminating the prothrombin preparation is insufficiently elucidated in these and many other thromboplastic studies. Myelin-figure formation from the above-mentioned brain phosphatides, especially cephalin, yields information as to the peculiar mechanisms of lysis in platelets, megakaryocytes, and other formed elements (98).

(2) *Thromboplastic lipoproteins (thromboplastin or thrombokinas)*.—Lung extracts are a good source of these proteins. Howell's last work (143) was to isolate and partially purify what "appears to be a protein compound of a phospholipid." Intravenous injections caused marked and persistent reduction of clotting-time in blood from the strain of "hemophilic" pigs developed by Hogan, Muhrer & Bogart (134) but preliminary data suggest that it is not yet safe for human use. Chargaff *et al.* (36, 37) obtain an extremely active thromboplastic "lipoprotein" from beef lung. It is inactivated and insoluble after exhaustive extraction of its lipids, which are far less potent than the original substance. Marx & Dyckerhoff (213) also obtained a semi-purified "lung thrombokinas" containing protein and lipids. Their preparations showed some species specificity and were dangerous when given intravenously.

Brain extracts have been used as a source of thromboplastic lipoproteins. Many recent workers have tried to improve upon the preparation of crude brain thromboplastin for use in the Quick test (165). Hays & Lein (130) present quantitative data on beef brain thromboplastin and its isolated phospholipids at various stages of purification. Crude brain thromboplastin, of high cephalin content, is significantly better than saline for lowering the mortality of mice with burn shock (278), but aggravates the death rate if given too late (86).

Placental preparations (108) have the advantage of being human proteins and therefore less likely to cause allergic reactions (77). Copley (46) has a potent new placental preparation, recommended for local hemostasis and for the *in vitro* coagulation of hemophilic blood, but it is risky in systemic administration (as shown by dog experiments). It contains much calcium, in addition to lipids and proteins.

Plasma and serum preparations have also been used. The Har-

vard workers (327) distinguish between two plasma fractions, (a) a "pseudoglobulin" which is principally thrombin, and (b) "globulin substance" (euglobulin) which is thromboplastic and contains tryptogen. Feissly, who had previously (87, 88) supported the enzyme idea, now (89) denies any role of plasma protease in prothrombin activation and claims to have obtained a "plasma-thrombokinas" devoid of proteolytic activity but having "a thermolabile phosphatidoproteic" link. He raises new questions as to the role of plasma proteins in hemophilia (90). Other European workers have been advancing along similar lines, with Reichel (267) supporting Lenggenhager's claim (182, 183, 184) for a plasma precursor ("prothrombokinas") requiring activation by wettable surfaces or a fall in carbon dioxide tension. Laki's "plasmakinin" (176) is another attempt to identify a protein-phospholipid thromboplastic agent in plasma.

Platelet preparations have not yet been subjected to modern methods of fractionation but also need restudy of the lipoprotein *vs.* enzyme possibilities, since Iyengar (151, 152) claims they contain tryptase and tryptokinase. Their thromboplastic activity has been correlated with an alleged abnormal stability in "bleeders" (238).

Saliva and urine are again referred to (115) as sources of thromboplastic factor and also require reconsideration in terms of tryptase enzyme (158).

(3) *Thromboplastic enzymes*.—Evolution of ideas relating to a thromboplastic function of certain proteolytic enzymes, with an important role in blood coagulation assigned to serum (and other) tryptase, is briefly reviewed by Ferguson (95). Parallel development of similar ideas by Tagnon *et al.* (327) brings out many points of fundamental agreement. In the analogous (but unrelated) system of pancreatic enzymes (245), trypsinogen is activated to trypsin with the aid of a kinase (e.g., enterokinase, mold kinase) and the active enzyme can be neutralized by combination with a polypeptide trypsin-inhibitor. In the case of the blood tryptogen-tryptase system (95) isolation of component factors has barely commenced, but there are preliminary data (93, 288, 289) to uphold the analogy, and unlooked-for progress has come indirectly from a study of bacterial (streptococcal) "fibrinolytic" mechanisms, which are deserving of special review in this connection.

Fibrinolysis and other proteolytic phenomena have been studied (95). The thromboplastic action of natural proteases is only a minor part of their total physiological significance and their major role, namely to digest proteins, is also important in blood coagulation, if we are to follow the process through to clot-retraction and clot-resolution (fibrinolysis). Furthermore, failures in the clotting mechanism are, at times, attributable to lysis of the essential protein clotting factors (prothrombin, thrombin, fibrinogen). Technical difficulties in isolating these proteins in stable form are largely due to effects of contaminating protease. Following the lead of Milstone (227), Christensen (39, 40) and Kaplan (160, 161) have clearly shown that streptococcal "fibrinolysin" is a misnomer for a factor which is really a kinase activator ("streptokinase") of the plasma enzyme (serum tryptase) which, when activated, not only lyses fibrin but also digests numerous other proteins. Holmberg (135) expresses similar views. Crystalline trypsin-inhibitor inhibits fibrinolysis, but as an antiprotease, not an "antifibrinolysin" or antikinase, as Mirsky (230) sees it, as well as blood coagulation (94, 125). The trypsin-inhibiting effects of heparin (118, 140) require unphysiologically large amount of heparin and may involve two mechanisms, (a) on enzyme, and (b) on substrate (141). Horwitt's recent studies (141, 142) compare heparin with hexyl-resorcinol and trypsin-inhibitors, (a) crystalline (pancreatic) and (b) serum. The greater potency of the last named "makes it hardly likely that the antitryptic action of heparin is an important factor in its physiological action." Horwitt concludes that the really significant plasma (serum) trypsin-inactivators are as yet unidentified. Ferguson's clotting theory (95) is alert to these possibilities of a complex plasma tryptase (thromboplastic enzyme) system and for the present, makes no claims as to the exact mode of activation but merely notes that the demonstrable excess of trypsin-inhibitors in plasma and role of colloidal (surface) adsorption in localizing tryptic actions (96) are suggestive evidence for the supposition that a primary activation of serum tryptase initiates the clotting phenomena in shed blood. Kaplan's work (161a) with the Harvard investigators (327) identified tryptase-precursor in the thromboplastic "globulin substance" (from plasma) and his current studies (160, 161) rank this material with Milstone's "lytic factor" preparations (227) as a source of the plasma proteolytic enzyme. Dycker-

hoff & Jakober (72) also discuss "fibrinolysin" in relation to blood clotting mechanisms, and Nolf (242), pioneer in this field, retains his original views, which should be reinterpreted in the light of the foregoing.

*Antiprotease and antifibrinolytic mechanisms.*—Kaplan (161) shows that a clear distinction must be made between true "antifibrinolysin" or antikinase (immune-specific neutralizer of streptokinase), and "antiprotease" (inhibitor of the active tryptase). By suitable tests the antifibrinolytic titer can be determined on human convalescent sera and is found to vary with strain of infective microorganism. The antiprotease titer, on the other hand, varies normally with animal species, which probably accounts for non-specific "antifibrinolytic" effects (so reported) in the literature. The titer is usually elevated during the acute febrile phase of the infection (124a). Christensen & MacLeod (40) give old references and use the fact that most of the antiprotease is in the albumin fraction of serum, which fits in with a recent note (30) that the antitryptic titer varies (*inter alia*) with the albumin-globulin ratio.

*Additional work on proteolytic enzymes in relation to blood coagulation.*—Crystalline trypsin, cautiously injected intravenously into hemophiliacs (321) does shorten clotting-time [in support of the theory advanced by Ferguson (91) and Tagnon *et al.* (323)] but the minor degree and duration of effect, together with obvious dangers of intravascular clotting and anaphylactoid shock, argue against any immediate therapeutic application. That these two toxic effects of intravenous trypsin are separable is emphasized by the actions of heparin, which prevents only the clotting complications, and of histamine, which duplicates many of the effects common to trypsin- and anaphylactic-shock, especially those which are not antagonized by heparin (69, 232, 351). Chymotrypsin produces only the latter, not the coagulation disturbances (324). Trypsin-inhibitor is antibiotic and penicillin, actinomycin A, and tyrothricin are weakly antiproteolytic, whereas synthetic detergents are both antiproteolytic and germicidal (231).

Menkin's "necrosin" (220) has proteolytic powers suggesting a tryptase, and it is probable that a similar factor is responsible for (a) the fluidity of menstrual blood (145, 201) and (b) the toxicity of menstrual discharge and of woman's blood during menstruation, pregnancy toxemias, and postoperatively as determined from animal injection experiments (308, 309, 310). Similar enzymes are



found in prostatic secretion (144), saliva (158), etc. Ficin is an anticoagulant because of its rapid proteolysis of essential clotting factors (33). Papain, which unlike trypsin clots fibrinogen directly (76, 100) before digesting it, is inhibited by serum (255). Staphylococcal "coagulase" (199), best assayed by a plasma-agar plate method (268), may need a serum factor (311), but is usually stated to clot fibrinogen directly (113, 215). There is some doubt whether a true fibrin is formed (188).

Animal venoms are reviewed by Essex (79) who notes their impurity and lack of uniform activity. Blood-coagulating and proteolytic activities are in the same (albuminoid) fraction and some venoms have been tried as hemostatics (206, 251). The coagulant action of bee-venom is noted (74). Russell viper venom ("stypven") is being tried as a substitute thromboplastin in PCT tests (170). Croxatto (51) studied three coagulant snake venoms and noted tryptase activity, although they did not attack his fibrins. Hargreaves (127) clotted fibrinogen with Jararaca venom plus calcium, allegedly without the intervention of prothrombin. Moccasin venom contains a phospholipase which partly hydrolyzes cephalin and some other phosphatides, liberating unsaturated fatty acids (83).

"*Heparin tolerance.*"—This is the difference between serial clotting-times (capillary blood test) before and after the injection of 10 mg. heparin, used as an index of thromboplastic function in clinical evaluation of thrombotic tendencies and anticoagulant therapy (64, 350). De Takats (62, 63) finds the response to heparin biphasic and influenced by autonomic drugs, and by digitalis (65), but Moses (237) finds the test unaffected by digitalis, epinephrine, and major surgical operations.

#### CLOT-INHIBITORY FACTORS

Preceding sections of this review have covered: (a) avoidance of wettable surfaces, (b) use of decalcifying anticoagulants, (c) loss of clotting power due to proteolysis of essential clotting factors, and (d) action of tryptase-inhibitors.

"*Antithromboplastic activity.*"—This continues to be advanced by Tocantins (331 to 336) to explain clotting-time differences between normal and hemophilic plasma and the effects of adsorption and differences between glass and nonwetable (collodion, paraffined, or plastic) tubes. However, an alternative explanation on

the basis of Ferguson's theory could be that serum tryptase (needed to mobilize the phospholipid factor from its protein combinations) is more active in the normal, adsorbed, and "wetted" plasmas and the hemophilic lacks the active enzyme, rather than displays any "inhibitory" factor. As Tocantins (332) notes, in confirmation of Chargaff & Ziff (38) and Ferguson (92), salmine (protamine), like proteins, combines with cephalin and can deviate it from the prothrombin-activating reaction, as one of the several ways in which it exerts an "antiprothrombic" (first phase inhibiting) effect. In Ferguson's view, however, the important thing is the availability of cephalin in the presence of all sorts of proteins. Hemophiliacs do not show antiprothrombic or antithrombic increase.

The action of sulfur compounds has been studied. Even such simple agents as sodium thiosulfate ( $\text{Na}_2\text{S}_2\text{O}_3$ ) and sodium tetrathionate ( $\text{Na}_2\text{S}_4\text{O}_6$ ) have anticoagulant effects (61, 195), and so do organic sulfur compounds containing an -SH group (cysteine, glutathione, etc.) or ester-linked sulfuric acids, e.g., germanin, liquoid, moranyl, chlorazole dyes, etc., reviewed by Quick (260), but the agents of greatest physiological interest are the heparins and they correspond chemically to the last group being mucoitin (carbohydrate derivative) polysulfuric esters.

*Heparin.*—Chemical studies aimed at explanation of the anticoagulant activity of these compounds are reported (163, 269, 362) Heparin actions on the clotting system apparently depend upon the presence of a co-factor (heparin-complement) (263). Lam (177) explains the finding of normal PCT after heparinization as due to overcoming of its "antithromboplastic" action by the tissue extract added for the Quick test. From what we have said about the three types of thromboplastic agent and in criticism of Tocantins, this explanation is obviously inadequate. Heparin plus co-factor not only inhibit the first phase of clotting (cf. salmine) but also the second phase ("antithrombic" effect). In addition, platelets are preserved in heparinized blood. Thus, both cellular and plasma (fibrin) factors of thrombus formation are directly inhibited (cf. dicumarol), so that, without need for exact knowledge of its complex modes of action, heparin can be used rationally for the clinical prevention and treatment of thromboembolic conditions (131, 276). Rapidity of action is one advantage of heparin over dicumarol, with which it may be concurrently used (81). The inability to

give heparin by mouth and its variable effect due to renal excretion and heparinase-destruction in the body are disadvantages (349). Even intravenous or intrasternal (191) injections are hard to control, but a new subcutaneous method, employing Pitkin's menstruum, is a practical answer (197). Toxic overdosage is best treated by the physiological antagonist salmine, in the form of protamine-zinc-insulin (plus sugar). Heparin is valuable in blood vessel surgery (26) and continues to receive notice for prevention of abdominal adhesions (217). Its usefulness against frostbite (and trench-foot) gangrene is limited to early cases (178). As an adjunct to the massive penicillin treatment of subacute bacterial endocarditis, anticoagulants are still *sub judice* (56, 133, 166, 196). Such protection as heparin affords against anaphylactic shock and the toxic effects of trypsin injections accrues solely from its anticoagulant, not antiprotease, effects (322, 351). Heparin formation by the mast-cells in the lungs is said to be interfered with in pneumonia (7). We are still uncertain how to evaluate the normal physiological role of heparin in relation to the coagulability of the blood (263).

Heparin-complement, antithrombin, and metathrombin are other factors to be considered. A method designed to measure heparin-complement (co-factor) is suggested (75). Wilson (359) compares the antithrombic activity of plasma and serum and finds important differences attributable to frequent lack of heparin-complement in serum. In the case of plasma, heparin elevates the antithrombic titer but this returns to normal on adding tissue thromboplastin and parallels the drop in the rate of thrombin formation. Heparin increases the thrombin inactivation by serum only to a degree determined by the quantity of thrombin left after the neutralization that has already occurred. "Antithrombic" action, therefore, is explained as an adsorption of thrombin onto certain proteins. In serum, the adsorbing factor is associated with the "albumin," whereas in plasma there is an additional, but essentially similar, heparin-activated protein (heparin plus co-factor). Work of this kind is important in confirming the modern trend away from a specific antithrombin (so-called) and toward the view that thrombin may be inactivated, "immediately," according to Glazko & Ferguson (117), by a more or less incidental participation in adsorption phenomena. Astrup *et al.* (10, 11) also advocate similar ideas in an earlier study of the relationships of heparin to antithrombin and find that the two components of the anti-

thrombic mechanism vary independently *in vivo* (12). Grüning (125) tries to implicate a lipid component in connection with the antithrombic activity of plasma albumin fractions. Lenggenhager's (182) "thrombin destruction rate" is a method, not very clear as to underlying principles, for allegedly following thrombin inactivation in defibrinated plasma. Recent users of the method claim longer time values when the albumin-globulin ratio falls (317) and in other conditions, clinically significant in cases of threatened thrombosis or embolism (239, 241).

"Metathrombin" is an old term associated with the idea of a specific combination of thrombin and serum antithrombin and the ability to recover thrombic activity with alkali and subsequent neutralization. Wöhlisch (361) adheres to the old concepts in a study of temperature and time factors, important because of loss of thrombic potency during and after the reactivation.

*Other anticoagulants.*—Besides sulfuric esters of cellulose (269), simple oxidized (absorbable) cellulose (112) is said to antagonize thrombin (293). Neodymium acetate, used in earlier studies (73) for comparison with heparin and other anticoagulants, is found unsuitable for clinical use because of dangers of hemorrhage, kidney damage, etc. (346). Tissue anticoagulants, obtainable by suitable fractionation, may owe some of their action to certain sphingomyelins (60). Amniotic fluid concentrates are useful in the prevention of abdominal adhesions postoperatively (221).

### HEMORRHAGIC DISORDERS

*Hemophilia.*—Nolf has a good review but a heterodox explanation of hemophilia (242). We have mentioned the reasons for doubting Tocantins' explanation on the basis of "anticephalin" increase and for preferring the hypothesis (91, 323) of a tryptase enzyme deficiency, confirmed by the (experimental) effectiveness of crystalline trypsin *in vitro* (91) and *in vivo* (321). The new fibrin-thrombin hemostatics are available for local control of bleeding in hemophiliacs, e.g., during tooth-extraction (148) and autogenous skin-grafting (54). The enzyme hypothesis needs more searching investigation not only in true hemophilia but also in ostensibly similar thromboplastic disorders, e.g., the reported hemophilia-like condition in woman (208), and the "hemophilia" of a unique strain of pigs, that responds to the thromboplastic preparations of Howell (143) and Copley (46). Waning interest in the possible

relationship of sex hormones to hemophilia (23, 24, 25) is weakly revived by a recent claim (339, 340) that estrogens (including stilbestrol) ameliorate, while progesterone and androgens aggravate, the disease.

*Purpuras.*—Purpuric bleedings are not coagulation disorders but depend upon platelet and capillary factors. Coagulation is indirectly involved, however, (a) to take care of the extravasation and (b) secondary to the systemic disturbance, particularly when it involves liver functions concerned in the production of clotting factors (see scurvy). Capillary resistance tests (209, 342), platelet counts, and megakaryocyte counts of sternal puncture bone-marrow (281) add to the diagnostic information given by bleeding-time (342) and clotting-time tests. There are still questions as to the role of the platelets in the mechanical plugging (the cell-factor in thrombus formation), in clot-retraction (see fibrinolysis), and the significance of undue platelet stability in "bleeders" (238). Tocantins' review (330) is excellent background reading for evaluating current work on platelets. Thrombocytopenia cases are reviewed by Evans & Perry (80) and MacDonald *et al.* (205) note a relationship to thermal burns. There are reports on the very rare congenital thrombocytopenia (235, 285). Quick discusses four ways in which drugs can cause hemorrhages (264).

*Vitamin P.*—This alleged factor in the control of capillary fragility continues to attract attention (247, 256). There are discussions of bioassay methods (119, 167, 209). To the current list of flavone glucosides (e.g., citrin, hesperidin, etc.) must be added another, from tobacco, viz., rutin (123). French workers (180), however, argue for epicatechol (3,5,7,3',4'-pentahydroxy-phenylbenzo- $\gamma$ -puran). Ungar's guinea pig studies apply standardized techniques for capillary resistance and bleeding time to learn the effects of trauma and drugs, including vitamins C and P (342). Experimentally (28) and clinically (284), vitamin P (citrin, hesperidin) is advocated for scurvy, to supplement vitamin C. It can be tried in nonthrombocytopenic purpuras (247), ocular hemorrhage (218), diabetic (279), and hypertensive bleedings (124).

#### SUMMARY OF PHYSIOLOGICAL PRINCIPLES OF HEMOSTASIS

*Systemic hemostasis.*—This is still an elusive goal. Rational treatment of bleeding disorders calls for elucidation of causative factors and specific correction as far as knowledge and availability

of agents permit. The extent to which this is currently practicable in deficiencies of the liver, of fibrinogen, of prothrombin, of vitamin K, and of thromboplastic factors has been reviewed. In many instances, however, hemorrhage treatment, apart from vasoligation, tamponing, and other surgical intervention, including life-saving transfusions of whole blood, plasma (250), etc., is still largely a matter of the body's own defenses of cellular and thrombic clotting mechanisms. There is no intravenous hemostatic, as yet, which is safe and efficacious. When blood or plasma transfusions are used to supply clotting factors (*inter alia*), the lability of the latter on keeping blood or plasma outside the body must be borne in mind (328).

Thromboplastic "globulin substance," given intramuscularly, or perhaps intravenously, gives some relief in hemophilia but patients soon become refractory (327). Being human in origin, fractionated plasma and placental preparations offer most hope for the future (229) but current progress herein reported is not too encouraging. There has been a similar but limited experience with certain snake venoms (206). The empirical use of dicarboxylic acids (210, 316), e.g. "koagamin," still has a few supporters (32, 132). Extracts of a Mexican herb, *Commelina pallida*, decrease coagulation time *in vitro* and *in vivo* (252).

*Local hemostasis.*—This requires consideration not only of the physiological effectiveness of the coagulant used but also of problems relating to accessibility of the bleeding points and to mechanical control (e.g., vasoconstriction, tamponing, etc.) of the blood pressure behind the leak. Thrombin is leading the field of successful local hemostatics, especially in conjunction with the mechanical and protective support of fibrin foam, fibrin films, "gelfoam," and oxidized cellulose. Next come the thromboplastic preparations, e.g., placental, with more variable reports of success. Detailed evaluations of the various clinical applications are outside the scope of this physiological review.

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## BLOOD CYTOLOGY\*

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This review of the extensive literature on the blood appearing from July, 1944, to July, 1945, is of necessity greatly restricted. Allotment of space did not permit, in some instances, more than a reference and, in others, more than a mere statement of certain conclusions drawn. Critical appraisals were not made but a survey and condensation of the literature for those investigators who may wish to consult the originals for details was undertaken. Although war has restricted investigation in certain subjects, it has stimulated it in others; so that some of the current literature concerns problems growing out of the world conflict. Although efforts were made to make this review as complete as possible, it is realized that valuable contributions have been overlooked. For these omissions and for what may appear to authors to be too brief reference to their papers, apologies are humbly offered.

### REVIEWS

Comprehensive reviews of clinical hematology, wherein 626 articles were cited, were assembled by the staff of Simpson Memorial Institute at Ann Arbor, Michigan (1, 2, 3). Certain clinical anemias, including the deficiency anemias, were reviewed by Dameshek (4) and Britton (5). The pernicious anemia of pregnancy was reviewed by Callender (6). The leukemias, with hypotheses of origin, were reviewed by Miller & Turner (7); the acute and chronic myeloid and lymphoid leukemias, by Haden (8); and the experimental mammalian leukemias, by Kirschbaum (9). A review of the chemical and physiological action of anticoagulants, notably heparin and dicumarol, effective *in vivo*, was made by Quick (10). Plasma proteins were reviewed by Elman (11).

Because of the recent clinical interest in isoimmunization, a number of reviews have appeared in the literature on the Rh factors and their relation to transfusion problems and to the syndrome of

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erythroblastosis fetalis. These include reviews by Potter (12), Diamond (13), Strandkov (14), Davidsohn (15), Pieri & Schwartz (16), Diamond (17, 18), Levine (19), and Wiener (20).

#### TECHNIQUES

A polychrome stain which possesses all fundamental requirements of a single process stain has been described; it required no mordant and resulted in minimal shrinkage (21). A self-buffering staining solution provided a convenient and practical method for buffering methyl alcohol solutions of polychrome methylene blue-eosin stain (22). The factors which modify the results of the selective staining reactions of Wright's stain, long a matter of concern to hematologists, were discussed. Variations in color reactions by the cellular constituents hinged on the basic component of the Romanovsky stain (23). The Prussian blue reaction of non-hematin iron was considered questionable and a new method using dipyrindyl and potassium thiocyanate in 1 per cent hydrochloric acid was recommended (24). The use of propylene-glycol aqueous stains as white blood cell diluents provided sufficient differentiation to determine the polymorphonuclear, eosinophilic, and mononuclear leucocyte percentages directly in the counting chamber (25). In histological sections eosinophilic granules stain less precisely than in blood smears. Adding chromotrope 2R to phenol crystals, a staining solution was prepared which more effectively stained eosinophilic granules. Paneth cells and enterochromaffin cells were readily distinguished (26).

By using a modification of the method of Flink & Watson for fecal hemoglobin, a more satisfactory method for determining hemoglobin in tissues, such as the lungs, heart, and liver, was devised (27). Errors in hematocrit determinations result from divergent methods of collecting blood, from the use of various anticoagulants, and from differing temperatures and speeds of centrifugation. A need for standardization of these procedures was stressed (28). A simple method for making imprints and smears of aspirated sternal marrow, consisting of free cells and gross marrow units, was described (29). When plasmas are turbid or lipemic, volume determinations are often difficult. By using a method involving the selective adsorption of the Evans blue dye on aluminum hydroxide and magnesium oxide, such difficulties were avoided (30). The dye method and the carbon monoxide method

were used to determine blood volumes in human beings and in dogs. These methods gave average values which were practically identical (31). In pathological states the same general results were obtained. It was concluded that neither method consistently measured absolute blood volume but direction of changes was consistently indicated by both methods (32).

#### GENERAL CONSIDERATIONS

Wide disparities in blood data in the newborn arise from differences in techniques and from sources of blood, whether cord, heel, or sinuses (33). Total erythrocytes, hemoglobin values, and cell volumes were higher in heel than in cord blood. There were no relationships between the erythrogram and the weight or sex of the newborn (34). Erythrocytes, hemoglobin values and leucocytes, their total and relative distribution, were computed for the hamster (35). Quantitative data on the blood and bone marrow of newborn puppies and adult dogs indicated that the average normal value for hemoglobin in either puppies or adults was nearly 18 gm. per 100 cc. of blood (36, 37). Likewise in the rat the total mean corpuscular hemoglobin did not change with growth (38). Erythrocyte, leucocyte, and hemoglobin values for the horse were reported. The leucocyte count and the Schilling index proved valuable prognostic data (39).

Centrifuging rat spleens at 400,000 g for thirty minutes showed stratification of erythrocytes into two or three layers, indicating that red cells are composed of at least three discrete substances differing in relative specific gravity (40). Formulas were derived for the mechanical fragility of red cells and such factors as spheroidicity and cohesion were studied in their relationship to fragility (41). Reticulocytes were tested for their phosphorus content. The concentration of adenosinetriphosphate had increased from levels of 10 mg. to 30 mg. per 100 cc. of blood (42).

Erythrocyte sedimentation rates prove to be valuable diagnostic data (43, 44, 45). Increases in rate occurred with the elaboration of serum globulins and plasma fibrinogen (46) and with additions of desoxyribonucleic acid, gelatin, or hyaluronic acid (47). Advantages of calculating the concentration of cellular elements in terms of molecular populations were set forth with formulas to calculate the molecular populations of hemoglobin, of glucose, of dissolved and bound oxygen, and of water in erythrocytes (48). Clumping

of erythrocytes in Hayem's solution appeared in various pathological states and was regarded as a grave prognostic sign (49). It is a true agglutination and may occur in such states as hyperglobulinemia (50). The mean concentration of hemoglobin declined in intact dogs anesthetized with pentothal sodium but only slight changes were observed in animals previously splenectomized (51). Hemoconcentration, previously reported to occur in dogs when etherized, but not in cats or rabbits, did not occur in adult female rats under ether (52). Hemoglobin, when given intraperitoneally, contributes to a protein pool from which the various proteins may emerge to supply the requirements of the tissues (53). Hemoglobin levels were observed to decline with the onset of spontaneous cancer in strains of mice with high incidence of mammary cancer (54).

Oxygen tension is an important factor in regulating hemopoietic activity. Immediate polycythemic responses to low pressures were due to the release of stored blood and to hemoconcentration but, under prolonged stimuli or constant exposure to low pressure environments, erythropoietic hyperactivity ensued (55). At altitudes of 4,000 meters there was an increased affinity of hemoglobin for oxygen (56). By means of an indirect gasometric procedure the degree of saturation of hemoglobin in arterial blood at sea level was found higher than hitherto accepted. Average values of 98.5 per cent for the dog and of 98.6 per cent for man were obtained (57).

Xanthopterin exerted a marked stimulus to erythropoiesis in young Chinook salmon (58). Basophilic stippling of red blood cells in lead poisoning was studied. Lead upsets the evolution of the proteins in the development of the immature red cell, resulting in the formation of the basophilic granules. Since these proteins are involved in hemoglobin formation, there are associated changes which induce the formation and elimination of coproporphyrin. Thus coproporphyrinuria accompanied basophilic stippling (59). A protein fraction, considered perhaps to be a glycoprotein, obtained from urines of chronic leukemic patients, was capable of causing myeloid hyperplasia in guinea pigs (60).

The number of formed elements in the blood is presumably associated with stimuli induced by the sympatheticoadrenal system. Adrenotropic hormone induced lymphopenia (61), leucocytosis (62), and a concomitant rise in serum proteins (61). The injection of adrenocorticotrophic hormone decreased the number of lympho-

cytes in thoracic duct lymph more than 50 per cent (63). These changes did not occur in adrenalectomized animals (63) or when intact animals were given pure protein (64). Metrazol induced neutrophilic leucocytosis in vagotomized rats but not in adrenodemedullated rats. Leucocytosis is considered to be due to a sympathetico-adrenal discharge. Typhoid-paratyphoid vaccine, however, acted directly on the bone marrow, inducing leucocytosis in either vagotomized or adrenodemedullated rats (65). Adrenotropic hormone acting on the adrenal cortex maintains a physiological control over the numbers of erythrocytes and leucocytes (66). Single injections of adrenotropic hormone increased total serum globulins (67). Suggestions were made that lymphocytes may be a storehouse for the globulin fractions and that their release is under control of the adrenotropic hormone (67).

A leucocytosis-promoting factor exists in exudates. It is thermolabile and is concentrated in the pseudoglobulin fraction. Necrosin, associated with the euglobulin fraction, may consist of two components. One is concerned with cellular injury; the other is pyrogenic. The fever accompanying inflammatory reactions may be due to the absorption of the pyrogenic component of necrosin (68). Since granulocytes contain histamine, a hypotensive agent, leucocytosis was induced in dogs previously made hypertensive by the silk method. Conclusions were indicated that leucocytosis is not a hypotensive factor (69).

Cows positive to the agglutinative test for brucellosis showed marked changes in their leucocyte picture after an injection of a filtrate prepared from *Brucella abortus* after ultrasonic disintegration. A rise in the percentage of immature neutrophils and an increase in the total white cell count occurred. Only normal variations occurred in cows negative to brucellosis after such injections (70).

Lymphocytes in tonsillar epithelia were derived from lymphoid tissue and not from the blood stream. Trends toward degeneration and fragmentation of these cells were observed within the epithelia (71). Fifty roentgen ray units induced a minimal cytotoxic effect on lymphocytes of thymus suspensions but granulocytes of spleen and bone marrow of rabbits and cells of myelogenous leukemic patients were resistant to 1,000 r (72). Lymphocytes produced antibodies and lymphoid tissue exerted a role in immunity (73). Agglutinin and hemolysin titers were obtained from washed cells of lymph nodes of mice immunized to sheep erythrocytes but titers of



extracts of salivary glands and muscle tissue were negative in all dilutions (74). Destruction of lymphocytes by roentgen rays reduced antibody formation while stimulation of lymphocytosis by dry heat increased antibody formation (75). Antibody titer of lymphocyte concentrates was always higher than the titer of lymph plasma. Conclusions were drawn that cells rather than plasma were instrumental in antibody formation (76). Plasma cells derived from plasma cell tumors were specifically related to cells concerned in antibody formation (77). When sensitized red cells were incubated at 37°C. for one hour with an activated papain solution the antibodies were completely destroyed and such cells lost their susceptibility to complement. They were, however, readily resensitized with a minimum of amboceptor (78).

Quantitative distribution of bone marrow was determined for rabbits (79). The total number of lymphocytes in the total marrow was computed to be  $2,330 \times 10^6$  (80). The origin of the lymphocytes and the routes by which these cells leave the blood stream were described (80). Hemoglobin stimulated blood regeneration but there was a distinct difference in the response of bone marrow explants to hemoglobin and to red cell stroma. Hemoglobin induced an increase in mature red cells, while red cell stroma induced an increase in the immature cells. Stroma produced an erythroblastic type of bone marrow *in vitro* (81). Human sternal marrow biopsies were practical diagnostic procedures, extremely useful in diagnosing parasitic diseases, leprosy, and certain infections (82, 83, 84). Volumetric determinations of human sternal marrow gave the following percentages: fat, 1 volume per cent; plasma, 44 volumes per cent; the myeloid-erythroid (M-E), 5 volumes per cent; and erythrocytes, 50 volumes per cent (85). Rabbits made leucopenic by giving 1 cc. of a solution containing five parts of benzene and one part of olive oil twice daily proved satisfactory test objects for assaying yellow bone marrow extracts (86).

Using the diazo dye (T-1824), plasma, blood, and cell volumes were determined in male rats (87); significant increases occurred with growth and with change in body size. Electrophoretic methods for plasma analysis gave values for albumin-globulin ratios appreciably less than those obtained chemically (88). By the same method fetal gamma globulin values were found to be higher than either normal or maternal values (89). Substances in blood serums and platelets stimulated the rat intestine and the vessels in the

rabbit ear but plasma, hemolyzed red cells, or lymphocytes were essentially without effect on these test objects (90).

### HEMOLYSIS

According to Ponder (91) the contents of the blood stream may be considered a hemolytic system, in which a balance is maintained between the production and the destruction of erythrocytes. The kinetics of red cell production and destruction are maintained normally in equilibrium by three hemolytic processes, including the action of bile salts, the role of the spleen, and the action of hemolytic substances derived from tissues (91). The "hemolytic index" is the relationship between fecal urobilinogen in percentage and the total hemoglobin and blood volume (92). Intravascular hemolysis may give rise to severe reactions, for when a 2 per cent solution of pure hemoglobin was injected into the veins of dogs, absolute neutrophilia, relative lymphocytosis, an increased sedimentation rate, and lengthened coagulation time were produced (93). Irradiation of fowl erythrocytes with doses of roentgen rays up to 2,000,000 *r* caused increased respiration. Hemolysis occurred when erythrocytes, previously irradiated, were incubated at 39° to 40°C. (94). Preirradiated erythrocytes not only were shown to be resistant to the hemolytic effect of roentgen rays but were resistant to light and saponin as well. This resistance depends on the concentration of the suspension and did not appear when serum was added or when the red cells were suspended in glucose (95).

In dogs in which a biliary fistula had been established, large amounts of iron, freed from the red cells after hemolysis induced by acetylphenylhydrazine, were eliminated by way of the biliary tract (96). Phenolphthalein did not decrease the resistance of red cells to saponin hemolysis; it was decreased, however, by a 2 per cent solution of sulfanilamide (97). A direct titration method giving a measure of the net antihemolytic value of whole blood in terms of lysolecithin was adopted. Changes in lysin concentrations were revealed by the amounts of lysolecithin required to induce hemolysis. The antihemolytic value was defined as the number of milligrams of lysolecithin required to induce a 50 per cent hemolysis of 1 cc. of blood in one minute at room temperature (98).

A review of the hemolysis due to snake venom was recently compiled (99). Venoms varied greatly in their hemolytic activity and erythrocytes varied in their susceptibility to venom. Lecithin

activated the hemolytic action of the venoms by the formation of lysolecithin, which induced solution of the corpuscular membrane of the red cell. Cholesterol induced changes in surface tension which effected a rapid separation of the stroma-hemoglobin union (100). Cold hemolysis is an irreversible phenomenon wherein hemoglobin may be liberated from erythrocytes at low temperatures. Cold hemagglutination occurred at temperatures below 25°C. and was entirely reversible on warming (101). Calcium exerts a marked effect on the permeability of cell membranes. In turtles immediate hemolysis of the red cells occurred in the absence of calcium. It was concluded that hemolysis was prevented by decreasing the permeability of the erythrocyte to other cations (102). A special protein substance in human plasma called "haptoglobin" was identified. The "haptoglobin index" varied with the various primary or secondary anemias and was low in cases involving hemolytic reactions (103).

#### EXPERIMENTAL HEMATOLOGY

Microcytic hypochromic anemias were produced in rabbits on a milk diet (104). This confirms earlier observations in man and the rat that iron and copper deficiencies produced microcytic hypochromic anemias. Using micromethods it was observed that there was a rapid turnover of nitrogenous materials in the bone marrow of iron- and copper-deficient rats during hemopoiesis (105). *Bartonella* anemia, rarely encountered in dogs, was reported to follow splenectomy (106). In rats made anemic by infection with *Bartonella muris*, serum potassium levels were increased because of a release of potassium by the hemolyzed red cells (107). Penicillin, in amounts equivalent to 400 units per kilogram of body weight, did not modify the mortality rate nor change the course of the anemia induced in splenectomized rats (108). Infectious anemias due to infestations with *Bartonella* were reviewed (109).

Testosterone accelerated red cell regeneration in anemic rats and augmented the response to administration of cobalt (110). Anemic dogs absorbed ferrous iron more readily than ferric. In man, ferrous iron was absorbed from one and a half to fifteen times as readily as ferric iron (111). These results were confirmed for man by using radioactive isotopes of iron (112). Red blood cells readily took up radioactive iron absorbed from the gastrointestinal tract. Twenty to 100 per cent of such cells, when given intraperi-

toneally to normal dogs, passed readily into the circulation through lymph vessels and lymph spaces but, when given to anemic or doubly depleted dogs, lower percentages were absorbed (113). The standard anemic dog with an Eck fistula was unable to utilize iron as efficiently as an anemic non-Eck fistula dog; so that in these animals the production of hemoglobin dropped to a fourth of that in normals (114). Repeated bleeding of animals fed a high fat diet resulted in cirrhosis of the liver, which was not produced by either bleeding or the diet alone (115). Parturient hemoglobinemia was produced in a cow fed a ration of alfalfa hay and dried beet pulp. This ration was adequate except for phosphorus and consequently hypophosphatemia ensued, which may have been responsible for the destruction of erythrocytes (116). Soybean lecithin produced a significant reduction of red cell counts in dogs, which was assumed to be due to the choline content of the lecithin. Choline, when given to dogs in amounts of 8 mg. per kg. daily, caused significant depression of erythrocyte counts (117). When lard was added to the diet of dogs, choline produced a more rapid reduction in the number of red cells (118). Liver, given intramuscularly, ventriculin, orally, and atropine, orally, induced return of the depressed levels to normal (119). Clinical reports, however, do not confirm the finding that choline depresses erythropoiesis (120, 121).

Chick antianemic activity of yeast is reported to be due to the presence of vitamin B<sub>9</sub> held in the form of a simple nonprotein conjugate (122). The properties of the enzyme which converts the conjugate to the vitamin were described (123). Ultraviolet absorption curves of vitamin B<sub>9</sub> were found to be essentially like those of xanthopterin (124). Folic acid activity in yeast was increased by incubating with fresh liver (125) or by autoclaving with either acid (pH 3.0 to 4.0) or 2*N* potassium hydroxide (126). There is need for some uniformity in measuring folic acid activity, for at least seven different methods are now being employed (127). A titrimetric assay for folic acid determination, using modified media and *Streptococcus lactis* R, was described (128). Folic acid may replace the *Streptococcus lactis* R factor, for growth of the organism in media containing the vitamin was essentially like that obtained when the factor was added (129). The distribution of the enzyme which produces the *Streptococcus lactis* R factor from its inactive precursor and the conditions for its action were discussed (130).

Granulocytopenia, observed in a small percentage of rats, was corrected in every case by crystalline *Lactobacillus casei* factor (folic acid) (131). Intramuscular injection of the *Lactobacillus casei* factor into three monkeys resulted in a prompt remission of the anemia and leucopenia which had been induced by a vitamin-M deficiency (132). Extracts produced from yeast, containing a factor convertible to *Streptococcus lactis* R factor, antagonistic to the succinylsulfathiazole effect in rats, were considered identical with vitamin M (133). Crystalline *Lactobacillus casei* factor both prevented and cured the anemia induced by sulfasuxidine in rats (134). When fed a crude ration, anemia was not produced in guinea pigs fed succinylsulfathiazole but it was produced when they were fed a fortified, purified diet (135). A panmyeloid arrest, induced in rats by a purified diet containing sulfaguanidine, was corrected by extracts of liver or by yeast with folic acid (136). Curative effects were induced in niacine-deficient dogs by a folic acid concentrate derived from solubilized liver extracts (137). A folic acid deficiency could not be produced in rats fed a milk diet low in folic acid, as tested by assay (138). Hydrogen peroxide-treated pyridoxine and the lactone of 2-methyl-3-hydroxy-4-hydroxy-methyl-5-carboxypyridine prevented chick anemia when a purified diet was supplemented with factor S prepared from strain S yeast (139). Later evidence showed that the *Lactobacillus casei* factor and either the 5-carboxy-lactone ( $\alpha$ -pyracin) or the isomeric 4-carboxy-lactone ( $\beta$ -pyracin) were required for the prevention of anemia in chicks (140).

Vitamin B<sub>6</sub> was as effective parenterally as orally, indicating that the influence of the vitamin on the chick anemia may not be mediated through changes in intestinal flora (141). An additional factor distinct from either growth factors R or S of Schumacher and co-workers was identified as a second chick antianemic factor. It may be identical with vitamin B<sub>6</sub> (142). An antianemic factor which prevented anemia in pigeons was found in the filtrate on treating a solution of liver extract with fuller's earth at a pH of 4.0 (143). Elevated serum iron levels, hemosiderosis, and microcytic anemia developed in pyridoxine deficiencies, because of some interference with the metabolism of tryptophane (144). Impairment of blood regeneration was prevented by pyridoxine (145). Tryptophane was thought to diminish the severity of the anemia due to pyridoxine deficiency induced in swine by feeding a synthet-

ic diet in which protein was supplied as an acid hydrolysate of casein (146). Clinically, pyridoxine was considered to be the maturation factor in the development of neutrophilic granulocytes (147, 148).

Bone marrow explants were not considered satisfactory test objects for determining the potency of liver extracts (149). Experimental thrombocytosis was induced by intravenous injection of pyridine or epinephrine. A stickiness of the platelets was observed after injection of pyridine but not after injection of epinephrine. Pyridine stimulated platelet production; epinephrine, their release (150). The mechanism of cobalt polycythemia remains unexplained but there was no impairment by cobalt of the respiration of bone marrow *in vitro* (151). In birds cobalt produced polycythemia, accompanied by marrow hyperplasia and an increase of extramedullary erythropoietic foci in spleen, liver, kidneys, and suprarenal glands, but on continuous injections the extramedullary foci disappeared (152). In dogs and in man, carbon monoxide produced polycythemia, wherein bone marrow stimulation with reticulocytosis and an increased percentage of normoblasts was observed. Its full development was not apparent until several days after the carbon monoxide had disappeared (153).

Intravenous injection of pyrogen produced not only fever, but primary leucopenia in sixty to ninety minutes. Leucopenia was considered a more sensitive indicator of pyrogen than fever (154).

Functions of cells depend on the coordinated activity of a number of elements. Cytoplasmic constituents of leukemic cells obtained from rats were fractionated by means of the centrifuge and chemical determinations were made. Mitochondria and microsomes were thus separated and the percentages of nitrogen, phosphorus, carbon and hydrogen and their lipid contents were determined (155). Leukemia was induced by carcinogens, roentgen rays, or estrogens but, on testing cancer strains, *A*, *F*, and *dba*, it appeared that susceptibility to any one leukemogenic agent did not indicate susceptibility to another (156). Doses of 200 *r* applied to black mice of strain C57 increased the incidence of leukemia from 7 to 30 per cent (157). The role of genes in the hereditary transmission of tendencies to spontaneous leukemia in mice was studied and genetic diversities sufficient to modify the incidence of leukemia were found (158). Underfeeding reduced the incidence of spontaneous lymphoid leukemia in a high leukemic strain from 65.0 to 10.1

per cent (159) and prolonged the duration of life. Age and sex were factors in experimental leukemia, for the disease developed more rapidly in males after sexual maturity than before and the incidence was greater in castrate males than in noncastrate (160). The incidence of leukemia in castrate males was 97 per cent; of intact males, 53.5 per cent; of ovariectomized females, 90.3 per cent; of ovariectomized females given testosterone, 58.3 per cent (161).

#### CLINICAL HEMATOLOGY

This review of reports of various blood dyscrasias encountered clinically is not intended to be inclusive but is restricted to those which were considered by their authors from physiological or pathological points of view. The anemias accompanying adenocarcinomas of the stomach included both macrocytic hyperchromic and microcytic hypochromic types. Their occurrence was probably related to associated hepatic insufficiencies rather than to factors causing Addisonian pernicious anemia (162). A chlorotic anemia was found associated with diaphragmatic hernia in 187 of 300 such cases reported (163). Anemias of chronic infections were dimorphic: one, hypochromic, related to the defective use of iron; the other, macrocytic, related to defective hepatic function (164). Red cells in patients with obstructive jaundice were increased in diameter but not in thickness and normal cells transfused into such patients assumed these same characteristics, which were thought to be induced by functional disturbances in the spleen (165).

Diagnostic symptoms of hemorrhage in man are few. Bleeding of healthy human beings showed that acute hemorrhage was not readily diagnosed by rapid pulse and low blood pressure, since recumbent subjects, bled to a point of collapse, did not exhibit conspicuous tachycardia (166). The spleen has long been known as a reservoir for sequestered blood. A new syndrome, "primary splenic panhematopenia," wherein the spleen may so harbor all blood elements as to present a clinical picture resembling panmarrow hyperplasia, was recognized. Splenectomy was recommended (167).

An anemia with elliptocytosis was observed in two brothers. The family history indicated that the condition was transmitted by unaffected females, either in the sex-linked manner of hemophilia or in the sex-influenced manner of baldness. It was refractory to customary therapies but splenectomy resulted in prompt decrease of elliptocytes (168). A case was reported of an intermedi-



ate type of ovalocytosis in which elliptical red cells became circular in sealed blood films. The addition of the donor's plasma to these sealed preparations restored the circular cells to their ellipsoid shape (169). The decrease in number of the various formed elements of the blood during pregnancy was shown to be due to a gradual uninterrupted dilution of the blood. From early pregnancy to a time five to eight weeks before term, dilution took place; thence there was increasing concentration of blood constituents (170). Among the dyscrasias encountered among infants born to diabetic mothers extramedullary erythropoiesis is well known. But newborn infants showed these same dyscrasias regardless of whether the mother was diabetic before or after delivery (171). Scurvy as an etiological factor in anemia has been questioned but of ten scorbutic patients recently studied eight were anemic and 500 mg. of vitamin C daily induced stimulation of reticulocytes in all (172).

Target cells derive their name from a resemblance to a "bull's eye" in stained films. They occur in hypochromic anemias which respond to iron and in anemias of thalassanemia major and minor which do not respond to iron. They may be produced *in vitro* by suspending red cells in plasma or serum rendered hypertonic. Rapid dehydration of a dog produced a significant increase in the number of target cells. Those occurring pathologically were rendered normal by suspending them in serum made hypotonic (173).

Shock resulting from anoxia was considered the causative factor in death from sickle cell anemia. Sickled erythrocytes are poor carriers of oxygen; they pack capillaries and thus result in loss of plasma and hemoconcentration (174). Sickling, a property inherent in the susceptible red cell, is encouraged by coagulation. Sickling is not related to variations in the electrolyte ionic balance, although available potassium may play a role in the sickling process. Sickled cells returned to normal biconcave disks on exposure to oxygen (175). Further evidence of the influence of oxygen on sickling was shown by the continuous inhalation of 70 to 100 per cent oxygen for eight to twenty days by patients with sickle cell anemia. Intravascular sickling declined but there were no detectable changes in the rate of hemolysis (176). Carbonic anhydrase probably does not enter into sickling beyond its function of facilitating the exchange of carbon dioxide and oxygen. Multiple washings of red cells removed substances essential for sickling. Zinc

acetate or sodium cyanide prevented the sickling process (177). Sickling rapidly increased when a drop of sickle-positive blood was mixed with a broth culture of a saline extract of human feces. The factor within the broth was thought to be an enzyme perhaps identical with or similar to the "blood group ferment" of Schiff (178).

Several sources of the vitamin-B complex contain the so-called extrinsic factor, which induce hemopoietic responses when added to gastric juice. The purification of crude casein, rendering it vitamin-free, eliminated the extrinsic factor. It was not restored to such casein preparations by the addition of pure vitamins. Opinions were maintained that the extrinsic factor is a thermostable component of the B complex, as yet unidentified (179).

According to Agren (180) the enzyme aminopolypeptidase is to be thought of as identical with the intrinsic factor of Castle. Obtained from vacuum-dried pyloric mucosa, the enzyme was purified one hundred fold and found effective when tested on pernicious anemia patients (180).

Diet is not considered a factor in initiating Addisonian pernicious anemia; racial factors best explain its distribution (181). There is little or no pernicious anemia in either China or Japan and the disease does not develop among full blooded Negroes; so that heredity emerges as the only adequate explanation and a genotype for pernicious anemia has been postulated (181). A contrary opinion resulted from the diagnosis of pernicious anemia in three Chinese; questions were raised as to the accuracy of earlier deductions concerning racial distribution (182).

Cholecystic disease is more likely to develop among patients with pernicious anemia than among normal persons of the same age group. In female patients the evacuation of the gallbladder was greatly retarded (183).

Macrocytic anemias which resisted parenteral therapy but responded to whole liver or yeast were thought to occur as a result of deficiency of nicotinic acid. Such depletion may reach stages wherein antianemic factors cannot stimulate blood regeneration. Nicotinic acid may be the factor which acts in those cases refractory to parenteral extracts but responsive to liver and to yeast (184).

Hematological data assembled from patients with certain macrocytic anemias demonstrated a prompt response to orally administered liver extracts after therapeutic failure with parenterally

administered liver extracts. Suggestions followed that some new hemopoietic substance may be formed within the digestive organs of such patients (185). Proteolyzed liver, a papain digest of whole liver, proved suitable for oral administration in cases in which anemias had proved refractory to parenterally administered extracts of known potency. In some of these the blood picture was macrocytic and the bone marrow megaloblastic, typical of true Addisonian pernicious anemia (186). However, in the nutritional macrocytic anemias such as pellagra and other B complex deficiencies, there was a prompt therapeutic response to purified extracts given parenterally (187). Deficiency dermatoses were encountered in patients with macrocytic anemias wherein deficiencies of the B complex were etiological factors (188). Ophthalmic defects were likewise correlated with the dietary deficiencies of pernicious anemia (sprue and so forth). Such defects may be due to changes in the chemical constituents of the blood resulting in hemostatic disturbances in capillaries and venules. Clinical symptoms improved on the parenteral administration of liver extract (189).

Correlating cardiac function with anemia, it was observed that moderate and temporary anemia exerted a beneficial effect on the heart, compelling it to develop some compensatory mechanism which allowed it to tolerate subsequent myocardial anoxia (190).

The etiological factor in infectious mononucleosis is a virus and the upper part of the respiratory tract is ordinarily considered the portal of entry. A case was reported wherein the disease with all typical symptoms, including a positive agglutination reaction, developed as a result of a cutaneous lesion following an insect bite. The role of insect vectors was considered (191). Cold hemagglutinins were identified in the serums of infectious mononucleosis patients. Those serums which did not contain active sheep cell agglutinins at 37° C. contained them at 5° C. (192).

The source of the circulating monocytes in mononuclear leukemias is now traced by Biggart to reticulum cells of spleen and lymph nodes. These may differentiate either into free motile histiocytes or into fixed tissue reticulocytes (193). Osseous lesions were identified in a monocytic leukemic patient and an osseous form of chronic monocytic leukemia was postulated (194). The peroxidase reaction was used to differentiate the acute leukemias into myeloblastic and lymphoblastic types. The reaction had value in that it

permitted a precise study of the stem cells involved (195). A patient who had chronic lymphoid leukemia was observed to have the characteristic blood picture but was without enlargement of spleen or lymph nodes. The disease was localized in the bone marrow, wherein the hemocytoblasts, subjected to some unknown influence, gave rise to lymphoid cells (196). The relationship of trauma to acute myelogenous leukemia was reviewed and data were submitted to show that superficial burns were precipitating agents in the production of leukemia (197). A true toxemia resulted from burns, inducing degenerative changes in the white blood cells which resembled toxic changes found in many pathological states (198).

No attempt is made to list the many reports which have appeared during the year on tropical eosinophilia. Brief mention, however, is made of a study wherein it was shown that in fifty-three of sixty-one cases of tropical eosinophilia the cold agglutinin reaction was positive. The significance of this reaction was not explained but a similarity between tropical eosinophilia and atypical virus pneumonia was recognized (199). High eosinophilic percentages in the bone marrows of patients with thrombocytopenic purpura were regarded as a favorable prognostic sign and were considered to represent an allergic state, of which the purpura was but another symptom (200).

#### EFFECT OF DRUGS

Occasionally, severe toxic reactions result from the use of sulfonamide drugs. Acute agranulocytosis developed in a patient seventeen days after 5 gm. of sulfanilamide had been placed in the peritoneal space (201). Leucopenia with neutropenia developed on the administration of sulfamerazine (202) and acute hemolytic anemia followed a course of sulfadiazine therapy, wherein the patient had received 59 gm. of the drug in eight days (203). In prophylaxis, sulfadiazine proved to have a greater suppressive action on the leucocytes of Negroes than on those of whites (204). The indiscriminate use of the various sulfonamides was discouraged. Agranulocytic angina with destruction of the bone marrow and disappearance of granulocytes from the blood stream followed the use of aminopyrine (205).

Although thiouracil has been used extensively in experimental medicine, untoward reactions on the blood have not been recorded.

In clinical use, however, there were unfavorable reactions in a few instances. Agranulocytosis was found to be due to an arrest of myeloid elements in the bone marrow (206). In a patient who had received 113.6 gm. of thiouracil in 128 days there were no granulocytes in the blood stream at death but the bone marrow was hyperplastic (207). In a survey of forty-three cases, one of agranulocytosis, one of granulocytopenia, and two of jaundice were described and the conclusion was drawn that thiouracil is an unpredictable toxic drug with untoward influences on the bone marrow (208).

Aplastic anemia was reported in three cases in which the patients had been exposed to dust and fumes of trinitrotoluene for several weeks (209). On the other hand, weekly blood counts on seventeen workers in intimate contact with trinitrotoluene for eight weeks showed no influence on either erythrocytes or hemoglobin values. Many showed transitory initial leucocytosis, accompanied by moderate eosinophilia, but toxic changes were not observed (210). Mapharsen, when administered as antisiphilic therapy, caused a thrombopenic purpura, wherein it was thought that platelets were not destroyed but temporarily sequestered in large capillary beds (211). Agranulocytosis was also produced by mapharsen (212). An acute agranulocytosis with complete absence of neutrophils developed in a syphilitic patient given combined arsenic and bismuth therapy (213). Atabrine in sufficient amounts to produce a yellow color of the skin induced eosinophilia of 8.4 per cent in malarial patients. An eosinophilic hyperplasia of the bone marrow ensued (214).

Acetanilid and acetophenetidin are analgesic and antipyretic drugs. A mild hemolytic anemia was produced in dogs by large doses but activity of bone marrow was not depressed. A temporary methemoglobinemia was produced (215). A transitory leucopenia and erythrocytosis were observed in rabbits and dogs given solutions of digitonin (216). Gold salts, when used therapeutically, had untoward effects on the blood system. Purpura, agranulocytosis, and changes in the reticuloendothelial system developed on their administration (217).

#### BLOOD GROUPS

The blood groups, A, B, O, M, N, and Rh, their subgroups and subtypes, their genetics and forensic implications were recently

reviewed (218, 219). Although forty years have elapsed since the four serological groups were identified, the chemical nature of their distinguishing substances remains unknown. Various materials which have shown blood group specificity have been isolated from peptones, pepsins, mucins, and so forth but the isolation of antigens from erythrocytes has not been reported (220). The observation that cells of a person of group B, when injected into rabbits, incited the production of antibodies which reacted with the antigen of group A confirmed the opinion that at least these antigens are chemically similar (221). The macroscopic method of blood typing was found accurate, for results were well within the range of error accepted by authorities (222). The usual procedure for testing has been to read tests after two hours at room temperature but it was learned that reactions were more rapid at 37°C. than at room or lower temperatures (223).

A purified nonantigenic substance which induced extremely potent immune bodies in rabbits was obtained from ovarian cyst fluid and converted into a complete antigen by conjugation with the protein component of the specific *O* somatic antigen of *Shigella dysenteriae* (224). In pooled plasma neutralization of the agglutinins occurred so that such plasmas may be given to persons of any type without serious reaction, as determined by the anti-A and anti-B agglutinin titers (225). For the first time a genetic linkage between a serological factor and a morphological factor for brachydactyly has been reported (226).

*The Rh factor.*—During the year numerous reports, both clinical and experimental, on the Rh factor and its role in the practice of medicine appeared. The entity erythroblastosis fetalis, including fetal hydrops, icterus gravis, and congenital icterus, may result from a reaction of the Rh-positive cells of the fetus to the agglutinins of the serum of an Rh-negative mother (227). Such pathological entities, however, may occur in infants born to Rh-positive mothers; so that suggestions were made that isoimmunization may be induced by the A or B agglutinogens, involving a mechanism similar to that established for the Rh factor (228). Early benign icterus, appearing within twenty-four hours after birth, may not be the entity icterus gravis. It is believed due to the passage of isohemagglutinins anti-A and anti-B from the mother to the child (229). A, B, and Rh-negative agglutinogens invoke an immune response between mother and child but anti-M or anti-N agglutinins only

rarely appear in the serum of a mother having a child of a dissimilar M or N type (230). Whereas there is a similarity between the syndrome of erythroblastosis fetalis and the dyscrasia of infants born to diabetic mothers, the Rh factor is almost invariably positive in these women (231). Both dizygotic twins born to an Rh-negative mother were Rh-positive. A severe hemolytic anomaly developed in one of the pair. The affected infant had a genotype of  $Rh_1rh$ , while the normal child had a genotype of  $Rh''rh$ ; so that the isoimmunization hypothesis was confirmed (232). Artificial insemination of an Rh-negative woman with Rh-negative spermatozoa resulted in normal offspring (233).

Using newer antigens, the percentage distribution of the Rh blood groups in a white population was determined as follows: negative, 14.3;  $Rh_1$ , 54.9;  $Rh_2$ , 15.6;  $Rh_1Rh_2$ , 12.0;  $Rh_0$ , 2.1;  $Rh'$ , 1.1;  $Rh''$ , 0.0. The corresponding gene frequencies in percentages were:  $rh$ , 37.8;  $Rh_1$ , 43.1;  $Rh_2$ , 16.0;  $Rh_0$ , 2.7;  $Rh'$ , 1.4; and  $Rh''$ , 0.0 (234). The hypothesis of the six allelic genes was reviewed and data were summarized regarding the distribution of the eight Rh types among white and Negro populations of New York City (235). The use of subscripts to designate alleles was considered inconsistent with modern genetic terminology; superscripts were considered preferable (236). Fisher's ingenious system of three allelomorphous antigens, named C, c, D, d, E, e, was employed to avoid confusion with other symbols (237) but the disadvantage in this duplicate system of lettering was stressed and advantages in a nomenclature involving a numbering of antisera 1 to 4 were observed (238). For the sake of uniformity and understanding, a vocabulary of twenty-one terms was employed to express new ideas and new facts about the Rh blood factors (239).

In addition to the six allelomorphs of Wiener,  $Rh_1$ ,  $Rh_2$ ,  $Rh'$ ,  $Rh''$ ,  $Rh_0$  and  $Rh$  (234), two others postulated by Fisher were described and provisionally designated  $Rh_y$  and  $Rh_z$  (240). Occasionally bloods were encountered which gave intermediate reactions, suggesting the existence of additional variants of the Rh agglutino-gen. These atypical groups may be determined by special alleles, such as those designated  $Rh_y$  (241). More recently in a report on the medicolegal applications of the Rh factor (242) the accuracy of the hypothesis of the six alleles (234) was accepted as beyond reasonable doubt (242). The medicolegal application of the Rh types is based on the laws of inheritance, whereby factors  $Rh_0$ ,



Rh' and Rh'' are transmitted as simple Mendelian dominants (242). Recently a new Rhesus antibody was described in a patient of group O having hemolytic anemia. This antibody has value in that it will permit a distinction between genotypes Rh<sub>2</sub>Rh<sub>2</sub> and Rh<sub>2</sub>rh, hitherto indistinguishable with commonly employed serums (243).

Anti-Hr serum (Levine), a rare anti-Rh serum, was thought similar to antiserum St, in that both reacted with Rh-negative and with a majority of Rh<sub>2</sub> cells. Recent evidence indicates that these serums contained quite different antibodies. Both reacted with Rh-negative blood but with different components of its antigenic constitution (244). Only 2 per cent of Rh-negative persons responded to Rh-positive blood by the production of iso-antibodies, while persons of blood groups A and B were regularly antigenic. This may be due to the fact that Rh is a subsurface antigen, while A and B are recognized as surface antigens. More recent reports indicate that there are fewer Rh hapten groups per erythrocyte than there are A or B hapten groups (245). Immune serums with Rh antibodies for testing purposes may be derived from three sources: (a) heteroimmune serums from guinea pigs; (b) isoimmune serums from Rh-negative persons transfused with Rh-positive blood; and (c) isoimmune serums obtained from Rh-negative mothers of children with erythroblastosis. The latter source was considered the only practical one at this time. Titer of anti-Rh agglutinins was highest eight to twenty days after delivery (246).

A simple, rapid, accurate method for Rh agglutination determinations employed 0.5 cc. of serum in a capillary tube with an 0.4 mm. bore. Such tubes were dipped into the agglutinating serum to allow it to enter. An equal amount of blood was then drawn in. After mixing, the tube was allowed to stand at an angle, incubated at 37.5°C., and read. Rh-positive blood formed a beaded layer along the lower margin of the tube (247). In attempts to find suitable preservatives for anti-Rh serum it was learned that merthiolate in concentrations of 1:5000 inhibited the action of anti-Rh agglutinins but did not affect the anti-A or anti-B agglutinins. Thus Rh antibodies were thought to be in a globulin fraction different from the one which carried the anti-A and anti-B agglutinins (248). The ascarid polysaccharide inhibited A and B agglutinins and was of value in the preparation of anti-Rh serums, in which

these agglutinins must be removed. In a test of a large number of anti-Rh serums from various sources the effectiveness of the ascarid polysaccharide was repeatedly demonstrated (249). An Rh antibody which combined with red cells *in vitro* but did not agglutinate them was called a "blocking antibody" (250) or an incomplete antibody (236). This antibody was specific for but one part of the antigen complex of Rh-positive cells and results showed that there was need for testing for this incomplete antibody in any serum of an Rh-negative woman in which anti-Rh factor was not found (251). Certain pooled serums contained an "inhibitor substance" or "blocking antibody," which interfered with the action of anti-Rh<sub>0</sub> serum, while others were found to contain "inhibitor substances," which interfered with the action of Rh<sub>0</sub>, Rh', and Rh'' antisera (252). The "blocking antibody" test proved valuable in detecting isoimmunization since Rh<sub>0</sub>-blocking antibodies may occur in Rh subtype testing serums (253).

The distribution of the Rh factor is normal in specific types of mental deficiency, such as Mongolian idiocy or spastic diplegia, but in undifferentiated mental deficiencies an abnormal distribution of the Rh factor occurred (254). Rh isoimmunization factors likewise are implicated in basal ganglion disease and in certain imbecile and idiot defectives (255). Further study of the relationships of Rh immunization factors to various states of mental aberration may prove enlightening.

*Racial distribution of the Rh factor.*—In white populations generally 84.3 per cent are Rh-positive. Among the Indian populations, 90.0 per cent were found to be Rh-positive (256); among New York Chinese, 98.5 per cent (257); and among New York Japanese, using standard anti-Rh<sub>0</sub> serums, 98 per cent were found to be Rh-positive (258). Of the Orientals in Hawaii 99.84 per cent were found to be Rh-positive (259); among Indonesians of Java and Celebes only two of 296 persons tested were Rh-negative, and it was presumed that in these two cases contamination with Spanish or Dutch blood had occurred (260). In India, 100 tests gave 98 per cent Rh-positive (261), results which were somewhat contrary to an earlier report (256). Among Fijians, 100 per cent were listed as Rh-positive (262). Among Mexicans, 48 per cent were found to be Rh<sub>1</sub>; 9.2 per cent, Rh<sub>2</sub>; 41.8 per cent, Rh<sub>1</sub>Rh<sub>2</sub>; and 1.0 per cent, Rh<sub>0</sub> (263).

## TRANSFUSIONS AND BLOOD SUBSTITUTES

The demand for blood and blood substitutes, in the extensive blood donor program, resulted in an extensive literature, a portion of which will be reviewed. To April 1, 1944, more than 7,000,000 pints of blood had been collected and processed without significant potential hazard to donors (264). Improved methods for processing bloods for transfusions in the Armed Services were described (265). The Blood Substitutes Subcommittee of the National Research Council critically examined every blood substitute; an appraisal of the therapeutic values of whole blood, plasma, serum albumin, gamma globulin, and isohemagglutinins has been made by Cohn (266). Massive transfusions of citrated blood were used in cases of extreme shock and were found satisfactory when replacement was made during a period of twenty minutes or longer (267). Thermal and allergic reactions occurred in recipients on receiving pooled plasmas but hemolysis did not occur. These allergic reactions, because of their protein nature, could not be avoided (268). Excellent results were obtained from transfusions among patients with severe articular disorders (269).

Plasma was regarded as the best substitute for whole blood and methods for its collection, centrifugation, and pooling were described (270). A paucity of plasma, anticipated on the cessation of patriotic motives to support the donor program, led to the suggestion that cadaver blood may well be used to augment plasma stores (271). Low temperatures do not render plasma proteins toxic, for transfusions with thawed plasma revealed no untoward reactions (272). A despeciated bovine serum, prepared from bloods collected at abattoirs, was reported to be an effective substitute for plasma in that it was nontoxic and free from antibodies and had an equivalent osmotic pressure (273). Pooled serums, although satisfactory substitutes in many ways, incited reactions of chills and fever in 27.5 per cent of the cases reported (274).

Need for the conservation and utilization of red cells, often lost in the preparation of plasma, was stressed (275 to 278). A 10 per cent solution of corn syrup in distilled water proved a satisfactory medium for suspending red blood cells (277). A solution called IBT, containing magnesium sulfate, potassium chloride, sodium chloride, and distilled water, proved in the hands of the Russians a satisfactory medium for suspension of red cells (279). Hemoglobin in Ringer-Locke solution or in plasma or whole blood diluted

with salt solutions proved a satisfactory substitute (280). A "modified globin," derived from hemoglobin obtained from packed red cells made available in the preparation of plasmas, had an osmotic pressure twice that of an equivalent amount of plasma proteins and proved a valuable substitute (281). A concentrated preparation of human white cells, when transfused, was highly effective in a case of agranulocytosis (282).

Macromolecular substances of varying molecular weights were used therapeutically in cases of shock and of septic infections. Methyl cellulose with molecular weights ranging from 32,200 to 143,000 resulted, when given intravenously, in leucopenia and other blood and organic dyscrasias (283). Gelatin, when given for shock, possessed the required qualities of a plasma substitute (284). Solution of gelatin gave a greater and a more sustained increase of plasma volume than physiological salt solution and was retained in the vascular bed a longer time (285). Gelatin increased plasma volume but there was no evidence that it had been metabolized (286). Given in an 8 per cent solution, 40 to 43 per cent was utilized and 60 to 57 per cent was recovered in the urine (287). Gelatin did not induce anaphylactic or other toxic reactions in doubly depleted dogs and was thought to contribute to formation of plasma protein and hemoglobin. Continuous administration of gelatin for several weeks, however, appeared to inhibit production of blood protein (288). The pseudoagglutination accompanying gelatin transfusions did not interfere with subsequent blood grouping procedures (289) nor with normal blood flow (290). Gelatin was found preferable to pectin in that less change was induced in tissues of various organs (291). Pectin produced splenomegaly with a peculiar deposit in the reticuloendothelial cells of the spleen and the liver (292). Dextran, a neutral, water-soluble polysaccharide, likewise satisfied the requirements for a plasma substitute (293). Shock induced in dogs by acute hemorrhage was not overcome by an amino acid solution or a hydrolysate of casein but suspensions of red cells in these solutions proved beneficial (294).

The importance of avoiding in transfusions possible isoimmunization reactions with respect to Rh factors was stressed. The Rh genotypes should be determined on all obstetric patients early in pregnancy (295). Hemolytic reactions have ensued in Rh-negative mothers transfused with Rh-positive blood (296 to 302). Isoimmunization may persist for years and result in extreme reactions

with complete destruction of donor cells within eleven days after transfusion (303, 304). The fact that blood was Rh-negative was not conclusive proof that untoward results of transfusion were due to the Rh factor. Sensitization to the Rh factor must be demonstrated (305). Isoimmunization to factor P, first described in 1928, resulted from repeated blood transfusions (306). Untoward reactions to transfusions with pooled serums resulted in episodes of "homologous serum jaundice" (307) and difficulties were encountered in distinguishing this entity from infective hepatitis (308).

*Bone marrow infusions.*—Bone marrow infusions were considered as routine procedure for children and infants. Their use for patients who had osteomyelitis, pyrogenic septicemia, or osteochondritis appears to be contraindicated (309 to 312). The intramedullary drip method for transfusing small children involved no risk and was recognized as a satisfactory alternative to intravenous therapy (313).

*Uses of blood products.*—The various fractions of human blood plasma have been used extensively in clinical and surgical practice. All constituents of plasma are not equally effective in the treatment of pathological conditions; therefore, fractionation programs are under way (314). Fractions thus far made available for use are fibrinogen and fibrin (for films and foams), immune globulins, isohemagglutinins, and albumins (314, 315). The time required for the absorption of various types of fibrin films implanted in muscle tissues of rabbits ranged from less than five to more than eighty days (316). Fibrin films prepared from fibrinogen and thrombin, in combination with sulfadiazine, proved effective in protecting denuded surfaces occasioned by burns in guinea pigs (317). Fibrin foams had the necessary characteristics of porosity, compressibility, and strength (318). They were resistant to bacterial fibrinolysis, were useful in neurosurgical procedures (319 to 322), and were employed in conjunction with sulfadiazine and penicillin (323). These plasma products have been used in radical mastectomy (324), in skin-grafting procedures (325, 326), and in prostatic surgery to control surface oozing (327). Oxidized cellulose used with these products of blood fractionation proved valuable as a hemostatic agent (328). Tensile strengths of plasma clots were decreased to about a half by dehydration by means of the high vacuum, low temperature techniques; the albumin-globulin ratio may also be altered (329). Plasma clots untreated with any anti-

coagulant were firmer and less subject to infections than treated clots (330). Clinically, the application of hemostatic globulin and plasma clot dressings to the local treatment of burns gave promising results for a more extended use (331). In addition to plasma fractions the use of red cells which contained some principle effective in stimulating tissue repair was indicated in surgical procedures (332). Various types of ulcers, infected burns, and granulating wounds responded favorably to a red blood cell paste (333, 334, 335).

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## THE LYMPHATIC SYSTEM

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### INTRODUCTION

It has been observed clinically, and the observations well substantiated by experimentation, that the lymphatic system participates in a great variety of physiological and pathological processes in which the well-being of the organism or its ability to survive is challenged. The lymphatic system displays a versatility of function; the well known role of the lymphatic system in the defense mechanism of the body in infection and inflammatory processes is only one phase of the more general scope of lymphatic physiodynamics. A wide variety of recent data attest to this claim, namely, the reciprocal relationship of physiological balance between the lymphatic system and endocrine tissues as seen in the syndrome known as the "alarm reaction," and in the more recent work indicating pituitary-adrenal control of the physiological activity of the lymphocyte, including the role of lymphatic tissue in the phenomena of immunity with evidence pointing to the formation of antibody globulin within the lymph node and possibly within the lymphocyte itself; and finally the role the lymphatic trunks play in carrying shock-producing toxins from wounds to the general circulation. In this review, the recent advances made will be described in detail; the older literature will be surveyed only insofar as it has a direct bearing on the more recent knowledge.

### THE LYMPHATIC APPARATUS AND THE ALARM REACTION

The "alarm reaction" is a syndrome or a sequence of events that occur with regularity when a severe injury is inflicted upon the organism. This syndrome is independent of the nature of the damaging agent and is "an expression of the general alarm of the organism when first confronted with a damaging agent" (1). It is a response of the organism when its homeostasis is challenged. Although various phases of this reaction had been noted previously in the literature, it was Selye (1) who first correlated the data, elaborated the concept with his own researches, and named the

reaction. One of the striking manifestations of this reaction to injury is the way in which the lymphatic organs participate, with concomitant changes in the endocrine glands. The lymphatic organs, thymus, lymph nodes, and spleen undergo rapid involution; the adrenal cortex hypertrophies, and there is loss of cortical lipoids and chromaffin substance from the adrenal medulla. The changes are most obvious in the thymus which decreases rapidly in size, the cells of the parenchyma disintegrate, and the connective tissue stroma of the organ becomes edematous. Involution in the lymph nodes usually begins in the germ centers which in a severe alarm reaction may disappear completely; the sinuses of the lymph node become engorged with erythrocytes. Involution of the spleen is less marked; it begins in the center of the Malpighian follicles, and the white pulp is more affected than the red.

In the course of an alarm reaction, unequivocal changes occur in the detailed morphology of the endocrine glands. In the adrenal, the cortex undergoes hyperplasia with a rapid loss of its lipid granules; the medulla loses its chromaffin granules and its cells undergo necrosis. In a severe alarm reaction no normal adrenal tissue may be found. All three lobes of the hypophysis and the pancreas show characteristic changes also.

The changes in the lymphatic organs in the course of an alarm reaction are inhibited by adrenalectomy, and to a lesser extent by hypophysectomy; they take place more rapidly after thyroidectomy, but thyroidectomy does not influence the inhibitory action which adrenalectomy exerts on the involution of the lymphatic organs. Estrone, when used to produce the alarm reaction, will cause involution of the thymus even after adrenalectomy. Castration normally results in hypertrophy of the lymphatic organs, but during an alarm reaction castration does not prevent the involution of the lymphatic organs. This interrelationship is of great significance, indicating a definite physiological balance between lymphatic tissue and hormonal influence, and it will be encountered again in the discussion of the recent work in regard to antibody globulin formation within lymph nodes.

#### ROLE OF THE LYMPHOCYTE AND LYMPHATIC TISSUE IN IMMUNITY

During the last three decades a variety of experimental data has been accumulating to show that the lymphatic system participates in the processes of immunity. The experimental work

done in developing and testing this concept has produced much factual information. Theories were proposed as explanations of various observed phenomena, only to have subsequent investigation render them untenable. But much of the earlier experimental data remains as a solid background for elaboration.

*Evidence of the formation of antibody globulin within lymph nodes.*—Among the earlier studies demonstrating the relation of lymphatic tissue to the processes of immunity are those by Murphy & Sturm (2) who showed that by subjecting rabbits to dry heat and thereby increasing the activity of their lymphoid tissue, the animals develop a higher titer of agglutinins and precipitins to various injected antigens; when, on the other hand, rabbits had their amount of lymphoid tissue reduced by x-ray treatment, the extent of antibody formation was decreased. Morphological changes in lymphoid tissue during the process of immunization were studied in detail by Hellman & White (3) who found an increase in total lymphatic tissue, with especial increase in size of the secondary nodules of the spleen and lymph nodes. They believed that the secondary nodules are centers reactive against bacteria. Carrel & Ingebrigtsen (4), as long ago as 1915, demonstrated the formation *in vitro* of hemolysins by using a tissue culture mixture of bone marrow and lymph nodes.

The most impressive and convincing of recent studies relating to this problem are those carried out by McMaster & Hudack (5). These investigators injected solutions of various antigens derived from killed cultures of bacteria intradermally into the ear of mice; they then excised and extracted the regional cervical lymph nodes, bled the mice, and determined the agglutinin titer in the extract and in the serum. Antibody appeared simultaneously in the lymph nodes of the injected side and in the serum on the seventh day following the injection, the concentration of antibody being higher in the lymph node extract. As the experiment progressed, antibody titer in nodes and serum increased, with the concentration of antibody always being higher in the lymph nodes. No agglutinins were found in the lymph nodes of the uninjected side until much later in the experiment when they also appeared in the spleen and in the extract of ear tissue on the injected side. These data would indicate that antibodies first appear in lymph nodes to be simultaneously discharged into the general circulation.

The possibility was considered that the antibodies might have

been formed elsewhere than in the lymph nodes and escaped from the general circulation into the inflamed interstitial tissues of the injected ear, there to be drained by the lymphatics to the regional lymph nodes. To test this possibility two sets of experiments were carried out. In one set it was shown that the inflammatory reaction in the ear produced by the injection of antigen had no effect on the results of the experiment. In another set of experiments, different antigens were injected into the right and left ears of mice and the agglutinin titer of specific antibodies several days later was determined in the sera and lymph node extracts from both sides. The lymph nodes on both sides were equally inflamed. It was found that "the concentration of each of the agglutinins was greatest in the lymph nodes on the side injected with the corresponding antigen and least in the lymph nodes on the opposite side. The concentration in the serum stood midway between the two. Had agglutinins been formed elsewhere than in the nodes, this distribution could not have occurred." The authors conclude that the formation of agglutinins within lymph nodes is clearly shown.

*Changes in the lymph node during antibody formation.*—Ehrich & Harris (6) analyzed the sequence of events within the lymph node during antibody formation. By the use of a rabbit in which the popliteal lymph node with its afferent and efferent lymphatics is exposed, these authors made a comparative study of antibody titers at the site of injection of antigen into the hind foot of the rabbit, in the afferent lymph, the lymph node, the efferent lymph, and the blood serum. Typhoid vaccine and sheep erythrocytes were used as antigens. Antibody titers remained low at the site of injection and in the afferent lymph but reached high concentrations within the lymph node; in some cases, the titers of lymph node extract and of efferent lymph were higher than those in the blood serum. The antibody titers in the serum thus are seen to have lagged behind those in the efferent lymph of the injected foot but reached their maximum in the serum after the peaks in the lymph had been passed.

The findings of Ehrich & Harris again lead one to the belief that antibodies are formed within the draining lymph node, and the authors divide the course of events in the lymph node into two phases. The first phase reached its peak three days after injection of antigen, and was characterized by the appearance in the lymph node sinus of granulocytic cells and monocytes. The granulocytes

soon disappeared due to phagocytosis and this was followed by diffuse hyperplasia of lymphatic tissue due to large numbers of small and medium sized lymphocytes, increase in weight of lymph node from 0.2 gm. to 1 gm. or more, and the output of large numbers of small lymphocytes through the efferent lymphatic vessel. The rise in the output of lymphocytes reached as high as 80,000 per cubic millimeter. These changes precede the antibody formation which ushers in the second phase. The latter phase appeared on the fourth day, reached its peak on the sixth to ninth day after injection of antigen, and consisted of the appearance of antibodies in the efferent lymph and serum, a further morphological change in the lymph node, namely, the development of large germinal centers, and the maintenance of the increased number of lymphocytes in the efferent lymph. Changes in the reticuloendothelial system in these experiments were inconspicuous and were in no way parallel to the antibody titers. These authors conclude that, in view of the inconspicuous reticuloendothelial changes and the enormous increase in lymphocytes in the efferent vessel which took place shortly before the antibodies made their appearance, the lymphocyte plays an important role in antibody formation.

*Activity of lymphocyte in antibody production.*—The question as to the nature of the cell engaged in antibody production is not new. An extensive literature has accumulated implicating the reticuloendothelial system in the formation of antibodies (7). Most of these studies point to the liver, presumably the Kupffer cells, as a source of serum globulins. The observations of Sabin (8) lead to the belief that antibody globulins come from the sacrifice of a part of the cytoplasm of cells of the reticuloendothelial system. Using a dye-protein which makes it possible to identify the cells by which it is phagocytized, Sabin found that after ingestion of this antigen by macrophages it is digested in the cell vacuole, rendered soluble, and passed into the cytoplasm itself. Coincident with the time when the dye-protein is no longer visible within these cells, antibodies appear in the serum and there is shedding of the exoplasm of the macrophages. The conclusion drawn by Sabin is that the passage of antigen into the cytoplasm in some way increases the synthesis of globulin within the cell and modifies some of it into antibody globulin. With the shedding of parts of the surface films of these cells both normal globulin and antibody globulin are carried into the circulation.

Sabin (8) points out, however, that Downey & Weidenreich (9) had described as a characteristic of lymphocytes a shedding of parts of the exoplasm and demonstrated this phenomenon in lymphocytes within the sinuses of lymph nodes and also in lymphocytes throughout the follicles. They later showed that the shed bits of cytoplasm were not platelets and that they disintegrated rapidly in the thoracic duct.

Opposed to Sabin's views on the reticuloendothelial origin of immune globulins are the studies by Rich, Lewis & Wintrobe (10) on the activity of the lymphocyte in the body's reaction to foreign protein. While studying the mechanism of hypersensitivity to foreign proteins, Rich and his co-workers were impressed by the enlargement of the spleen which occurred in animals receiving injections of nonbacterial foreign protein, such as horse serum or egg white. He found that, microscopically the splenic enlargement is due to large numbers of basophilic mononuclear cells that first appear in the Malpighian bodies and later spread out into the splenic pulp. The picture is identical with that found in the acute splenic enlargement caused by bacterial infection. These cells have been regarded by most investigators as histiocytes or reticuloendothelial cells; by studies of their manner of locomotion, however, Rich has found these cells to be identical with lymphoblasts. He states his case clearly:

(Our) studies provide a new type of evidence that the cells which proliferate so strikingly in the presence of foreign protein are lymphoid; and since these cells respond so promptly and in so specific a manner to the parenteral presence of foreign protein, it is tempting to suspect that they may be concerned in some way in the process of antibody formation. This has been suggested from time to time, but has been ignored by most writers, who prefer to regard the histiocytes as the probable producers of antibody. The latter view is, undoubtedly, an appealing one, if only for the reason that the histiocytes ingest foreign colloids so avidly, as shown by their phagocytosis of colloidal dyes. It has seemed reasonable to believe that the cells which take all kinds of foreign colloids into their body may be the cells which manufacture the antibodies against foreign proteins. There is, however, no actual evidence that the histiocytes produce antibody. Attempts have been made to interfere with antibody formation by overloading the histiocytes with various phagocytizable materials (the so-called "blockade of the reticuloendothelial system"), but the results have been highly conflicting, and even when positive are subject to a variety of interpretations.

The most recent study by Harris and co-workers (11) further analyzes the role in antibody formation played by the lymphocyte itself. Following the injection of antigen into the hind foot of the



rabbit, lymph from the efferent lymphatic of the popliteal lymph node was collected, the lymphocytes separated from the lymph plasma, and the antibody content determined in the lymphocyte extract and in the supernatant lymph plasma. It was found that the antibody titer of the cell extract was consistently higher than that of the surrounding fluid. It was also shown that antibodies were not absorbed or adsorbed by lymphocytes, and antibodies do pass from the cells to the surrounding lymph fluid to reach equilibrium, but not vice versa. These results appear to indicate that the higher antibody titer in the lymphocytes cannot be accounted for on the basis of adsorption from the lymph plasma, and, therefore, the cells themselves are involved in the formation of antibodies.

#### PITUITARY-ADRENAL CONTROL OF PHYSIOLOGICAL ACTIVITY OF THE LYMPHOCYTE

It is a characteristic feature of normal hematopoietic activity that the number of circulating lymphocytes in the blood stream is a physiological constant and stands within certain numerical limits. The exact mechanism by which this constant is maintained remains a mystery, although, on the basis of clinical observations, it has been suggested that the endocrine glands exercise a regulatory influence on hematopoietic activity (12). In a series of recent experimental studies, Dougherty & White and their co-workers have made observations which tend to show that (a) the regulation of the number of circulating lymphocytes is under control of the anterior pituitary gland, mediated by way of the adrenal cortex (13, 14); (b) functional and morphological alterations in lymphoid tissue are under control of adrenal cortical secretion (15); and (c) the rate of release of serum globulins from lymphoid tissue is under anterior pituitary-adrenal cortex control (16).

*Regulation of number of circulating lymphocytes.*—Dougherty & White (13, 14) injected adrenotropic hormone of the anterior pituitary into mice and studied the changes in cell pattern of the peripheral blood. Within the first few hours following a single injection of 1.0 mg. of the hormone there developed a decrease in the total leucocyte count due to a lymphopenia which reached its maximum nine hours after injection. During this period the number of polymorphonuclear leucocytes increased. After nine hours there was a gradual return to normal. Studies on the cholesterol

content of the adrenals of these mice revealed a progressive lowering of adrenal cholesterol level following hormone injection, the most marked drop occurring at the time when the induced peripheral lymphopenia is maximal. The concomitant downward trend of adrenal cholesterol content and lymphocyte count that follows pituitary hormone injection is striking. Rats and rabbits show more profound and lasting effects than mice. This response to adrenotropic hormone injection (except for the rise in polymorphonuclear leucocytes) is abolished following adrenalectomy, indicating that the effect of the hormone on the lymphocytes is mediated through the adrenal gland.

Similar results were obtained in mice, rats, and rabbits following the subcutaneous injection of aqueous adrenal cortical extract. There is a lymphopenia accompanied by a polymorphonuclear leucocytosis. This response to adrenal cortical extract is not altered by adrenalectomy.

Continued daily injection of adrenotropic hormone into mice also resulted in an absolute lymphopenia and an increase in polymorphonuclear leucocytes. Adrenalectomized animals, on the other hand, showed an absolute lymphocytosis and a depressed polymorphonuclear cell production. In evaluating the data of these experiments the authors state:

Although in these studies continued hormone injection produced a persistent lymphopenia, chronic adrenal cortical stimulation need not necessarily give a lymphopenic picture. It is not unlikely that continued accelerated lymphocyte dissolution is an incitant of lymphocyte production. This production may proceed at a rate greater than that of lymphocyte dissolution even though the latter process may be continuing more rapidly than normal. Thus the stimulus initially responsible for a lymphopenia may, if continued, cause a lymphocytosis. The production of a lymphocytosis could result from the gradual exhaustion of the adrenal cortex due to its prolonged stimulation. In this event, there would be a diminishing supply of humoral agents concerned with lymphocyte disposition, and the blood lymphocyte picture would alter in the direction of resembling that seen in an adrenalectomized animal.

*Function and morphology of lymphoid tissue.*—A close integration of physiological activity of the adrenal cortex and lymphoid tissue appears to have been established. In an effort to correlate the physiological activity of lymphoid tissue with structural changes that might take place, Dougherty & White (15) made a detailed histological analysis of lymph nodes, spleen, thymus, bone marrow, Peyer's patches, liver, kidneys, adrenals, and gonads,

following injection of either adrenotropic or adrenal cortical hormones. They found that structural changes take place in three phases, lymphocyte dissolution, repair, and recovery. Within one hour after hormone injection, retrogressive changes begin in the lymphatic tissues resulting in dissolution of lymphocytes and cessation of mitosis. The nuclei of the lymphocytes become pyknotic, the cells shed their cytoplasm, their number in the lymphoid tissue decreases, and there is edema of all lymphatic structures. These changes persist for six hours. The depletion of lymphocytes from lymphoid tissue is the combined result of arrest of mitosis and actual dissolution of cells. Mitosis in the remaining lymphocytes is resumed in the recovery phase which begins approximately nine hours after hormone injection. In this phase also reticular lymphocytes differentiate from reticular cells and mature. Within twenty-four hours the histological appearance of the lymphoid tissue is restored to normal. Prior to onset of recovery, and following shortly after the dissolution of lymphocytes has begun, comes the phase of repair characterized by phagocytosis of nuclear debris with deposition of dark basophilic material in the cytoplasm of fixed reticular cells and the appearance of large numbers of histocytes exhibiting a low degree of phagocytosis. This series of changes does not occur in adrenalectomized animals, indicating again that the action of the pituitary hormone on lymphoid tissue is mediated by way of the adrenal cortex. The effect of the adrenal cortex on the dissolution of lymphocytes is specific, inasmuch as the granulocytic or erythropoietic cells of the bone marrow did not show degenerative changes. It thus appears that the lymphocyte is an end organ of one aspect of adrenal cortical activity, and that the lymphopenia induced by adrenotropic hormone is in part the result of a failure of delivery of adequate numbers of lymphocytes to the circulation.

*Control of the rate of release of serum globulins from lymphoid tissue.*—Dougherty, White & Chase (17) have found that rabbits receiving adrenal cortical extract with antigen show higher final agglutinin titers than rabbits injected with antigen alone. Adrenal cortical extract apparently produces an augmentation of antibody titer late in the experimental period. Continuing their studies further (16) these investigators have observed that after a single injection of adrenotropic hormone, the total serum protein of the blood of mice and rats increases at the time that the lymphocytes

undergo dissolution, and that the increase is primarily due to a rise in the beta and gamma globulin fractions of the blood proteins. Furthermore, protein extracts obtained from isolated rabbit lymphocytes contain a protein with an electrophoretic mobility identical with the mobility of the gamma globulin of normal rabbit serum. From the time relationship that exists among histological changes in lymphoid tissue, blood lymphocyte level, serum protein concentration and antibody titers, it is concluded that a portion of the increased serum protein is antibody globulin derived from lymphocyte dissolution. These data, in the opinion of the authors, are further confirmatory evidence that lymphoid tissue is an important site of formation of blood globulins.

#### DISCUSSION OF ALARM REACTION AND PITUITARY-ADRENAL CONTROL OF LYMPHOID ACTIVITY

It is the opinion of the reviewers that Selye, and Dougherty & White, building on the isolated work of many others, have through their own experiments made classic contributions to the knowledge of the physiology of the lymphatic system. In his description of the alarm reaction based upon an abundance of varied experimental data, Selye has not only linked the endocrine and lymphatic systems but also has shown the acuteness of the changes engendered in lymphoid tissue by trauma. The correctness of Selye's deduction regarding the interrelation of trauma and the endocrine glands has received ample clinical confirmation (18 to 21). The exact meaning of the lymphoid changes remained unclarified.

The experiments of Dougherty & White fill the gap left by Selye, for their work synthesizes the alarm reaction and the observations of the relation of lymphoid cells to immune proteins. The data as yet available do not permit a final statement regarding the amount and nature of the proteins released from lymphocytes by adrenal cortical action. The rises observed in protein concentration in mice following injection of adrenal cortical extract are small. Even though consistent in the direction of change, they do not take into account sources of protein other than lymphocytes. Experiments recently performed in the reviewers' laboratory on the adrenalectomized dog suggest that the rise in blood volume and pressure in the insufficient animal, which follows injection of cortical extract, is motivated by the recovery through the lymphatic trunks of plasma protein puddled in the interstitial space.

It is possible that part of the rise in plasma protein observed by Dougherty & White following injection of adrenal cortical extract might be due to recovery of protein from places such as the interstitial space, not from the lymphocyte alone.

Though the nature and purpose of the globulin released by lymphoid tissue under adrenal cortical stimulation needs further elaboration, certain it is that the experiments of Dougherty & White leave little doubt regarding the cellular response of the lymphatic system to changes in endocrine function. It should be pointed out that there are clinical findings to substantiate the disclosures of Dougherty & White of the relation of the adrenal cortex to the number of lymphocytes circulating in the blood stream and to lymph node hypoplasia. An elevated lymphocyte count and hyperplasia of lymphoid tissue has been recorded in Addison's disease (22). In the reviewers' series of patients with tumor of the adrenal cortex associated with hyperfunction, a lymphopenia has been the rule<sup>1</sup> and two of these patients who had uncontrolled staphylococcal infection failed to show inflammatory enlargement of the lymph nodes which would have been the rule in otherwise normal people with comparable infection.

#### LYMPH IN THE STUDY OF TRAUMA

During the war, investigators probing into the nature of wounds and the effects of tissue damage upon the organism have turned to a study of lymph recovered from various wounds. In the previous *Annual Review of Physiology* Drinker covered the work in this field published in the first two years of the emergency period. This included an account of the elaboration by himself and his co-workers of the description in 1931 by Field, Drinker & White of the rise in lymph flow and protein concentration from the dog's foot following a thermal burn. Though these studies were concerned mainly with the possible delay in wound healing due to plasma proteins coagulated in the wound, they also explored for noxious substances the lymph draining from burned legs of calves and dogs. Drinker also reviewed other work, including that of Alrich (23), Katzenstein, Mylon & Winternitz (24), and Blalock (25), dealing with possible toxins in lymph from trauma of various sorts.

<sup>1</sup> Our attention to the lymphocyte counts in these patients was stimulated by the reports of Dougherty & White.

Ever since World War I there has been confusion regarding the formation of toxic substances in damaged tissue and the relation of their subsequent absorption into the general circulation to so-called wound shock. Cannon's summary (26) of both clinical and experimental experiences of World War I left little doubt but that shock producing toxins were absorbed from battle wounds. In the minds of most, Dale's histamine (27) became associated with the toxin of tissue origin. Doubt regarding tissue toxins as a prominent cause of shock was first published by Blalock (28) who pointed out a possible technical error of experiments conducted during World War I. Observations were then reported from other laboratories failing to recover toxic substances and tending to incriminate, as had Blalock, loss of an effective circulating blood volume as the sole cause of shock.

With the advent of World War II, wound toxin again became an issue. Blalock (25) and others (23, 24) in their analysis of experimental shock were forced to postulate once again the absorption of a toxin.

In the last two years of this war the nature and source of toxins absorbed from experimental wounds have been clarified by a classic series of observations in dogs by Aub and his collaborators (29, 30, 31); infection has been linked to shock. Aub and his group were perplexed, as had been many others, by the inconstancy of the recovery of toxins. They had produced shock in dogs by rendering the gastrocnemius muscle ischemic for five hours, and after reintroduction of the blood supply had collected the interstitial fluid or lymph flowing from this muscle by placing a rubber sheath around it (30). Large quantities of clear, high protein containing fluid were collected which upon injection into another dog sometimes resulted in a profound, prolonged lethal drop in blood pressure. Repetition of the experiment and analysis of the fluid have substantiated the lecithinase, or alpha toxin, of clostridial organisms (*Cl. welchii*) as the toxin (31). *Cl. welchii* were recovered from the experimental wounds and were found to be generally distributed on the skin of dogs. These workers do not claim that clostridial toxin is the chief cause of shock. They point out that *Cl. welchii* are obligatory anaerobes, that if the experimental conditions exclude oxygen from tissue, either by shutting off the blood supply for as short a period as five hours or by tissue trauma, and the tissue is contaminated by clostridia, the formation and absorption

of toxin through the lymphatics may be a major factor in the production of shock.

The widespread distribution of the clostridial organisms on the skin of dogs has been confirmed by Langohr & Owen in the reviewers' laboratory and it has been found virtually impossible to make a wound in this animal and not contaminate the wound. They have further confirmed the Aub group in the importance of clostridial toxin to shock by showing in dogs shocked by the tourniquet method a disappearance of antitoxin in the blood following release of the tourniquet.

The skin of the human being and other laboratory animals is not as heavily contaminated with clostridia as that of the dog and the significance of Aub's observations on the dog to shock in other animals is not likely to be so great. But it is clear that when, during the course of experiments in dogs, wounds are made, clostridial infection and the absorption of clostridial toxin is a variable to be reckoned with. It is the opinion of the reviewers that Aub and his collaborators have found the major explanation of past discrepancies in regard to toxins in experimental shock in dogs.

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### CARDIAC OUTPUT AND DYNAMICS

In reviewing methods for determination of blood pressure in man, Hamilton concluded that standards currently accepted as normal were too low, and predicted a return to a more ample figure (1, 2). This prediction, based largely on a critique of the acetylene method and the evidence that significant recirculation of blood from the coronary and systemic circulations begins within ten seconds after commencement of respiration with the gas, has already had a large measure of fulfillment. Cournand *et al.* (3, 4, 5) report the extension of their work to include, among other things, observations on cardiac output by the direct Fick method in a group of thirteen normal healthy males in the basal state, in the course of which more than 260 catheterizations of the right atrium or ventricle were carried out without serious ill effects. Cardiac output in these subjects varied between a minimum of 2.12 l. per sq.m. per min. and a maximum of 4.01, with an average of 3.12. Stead and co-workers (6) report variations from 2.4 to 3.9 l. with an average of 3.3 l. per sq. m. per min. in nineteen determinations by the same technique on eighteen normal males in the basal state. These figures are very close to 27 per cent higher than figures obtained by the acetylene method (3) and the question naturally arises as to whether excitement, apprehension, or other emotional disturbances plays any part in these circumstances to yield abnormally high values. Cournand *et al.* (3) meet this objection by excluding from their study results from subjects showing abnormal pulse rates, accelerated respiratory rate, or increased oxygen consumption. The average pulse rate in subjects employed in the study was 66 beats per minute, which is in close agreement with results of more comprehensive studies of basal pulse rates. The average value for four subjects with increased oxygen consumption or elevated pulse rate was 3.43 l., suggesting that anxiety even when and if present does not significantly augment the values obtained. Stead and co-workers, however, obtained an average cardiac index of

<sup>1</sup> This review covers the period from July 1 1944 to July 1 1945.

5.5 l. in five subjects showing pulse rates above 82 beats per min. or a metabolic rate of plus 10. Also disquieting is the report by McMichael & Sharpey-Schafer (7) that by the slow intravenous infusion of epinephrine in minute doses (3  $\mu$ g. per min.) it was in one instance possible to increase the cardiac output from 4.5 to 7 l. per min. without change in heart rate or alteration in right atrial or arterial blood pressure. If this observation is confirmed, it will require reconsideration of the criteria for absence of anxiety effects.

Employment of the Fick method has permitted observation on many points of interest and doubt in human cardiovascular physiology. It is now well established that cardiac output falls by approximately 25 per cent when a recumbent subject assumes an upright posture (6, 7, 8). Light is also thrown on the mechanism of orthostatic hypotension. Warren *et al.* (9) report that removal of 300 to 900 ml. of blood by venesection or the pooling of comparable amounts of blood in the extremities by tourniquets has no significant influence on cardiac output in the recumbent subject and is not followed by peripheral compensatory vasoconstriction even though right atrial pressure falls markedly. Acute circulatory collapse occurred in three instances and was accompanied by marked fall in systolic, diastolic, and mean arterial blood pressure, but did not entail change in cardiac output. The authors conclude (a) that in normal circumstances atrial blood pressure is considerably in excess of that required for adequate filling of the heart, so that marked fall in venous pressure may take place without circulatory impairment, and (b) that the syncope that occurs in these circumstances is not due to failure of an adequate venous return but to failure of the peripheral resistance. This is the conclusion, also, of Barcroft *et al.* (10) who determined cardiac output by the direct Fick technique in human volunteers in whom fainting was induced by venesection or by pooling of blood behind a tourniquet. During the first stage of the procedure [contrary to the finding of Warren *et al.* (9)], they observed a progressive fall in cardiac output, although blood pressure was maintained by increasing peripheral resistance. During the actual period of fainting, cardiac output rose slightly despite an accentuated drop in blood pressure. This could only be interpreted as indicating that the peripheral resistance had suddenly fallen, and plethysmographic studies indicated an increase in the forearm blood flow, attributable to the muscles and not the skin. The authors suggest that the sudden vasodilata-

tion is of neurogenic origin, possibly initiated by alterations in right atrial pressure.

Brannon *et al.* (11) note that in anemic subjects cardiac output does not begin to increase until the hemoglobin level falls below 7 gm. per cent, or unless the oxygen content of the arterial blood is less than approximately 9 volumes per cent. With profound anemia (hemoglobin under 5 gm. per cent) cardiac output rose as high as 13.6 l. per min., and a maximum cardiac index of 7.9 l. per sq. m. per min. was obtained. Atrial pressure was unchanged, while peripheral resistance was greatly diminished. Shore, Holt & Knoefel (12) inject a note of caution in the acceptance of values for mixed venous blood withdrawn by catheter in the direct Fick procedure by demonstrating considerable differences in the oxygen content of paired samples withdrawn from the vena cava, the right atrium, and the right ventricle or combinations of them in dogs, indicating an incomplete mixing of venous blood even in the right ventricle. Holt (13) has employed the Fick and the Stewart techniques in a study of cardiac output in dogs exposed to increased (+ 8 to 16 mm. Hg) and diminished (-8 to 16 mm. Hg) intrapulmonary pressure. With increased pressure cardiac output fell off by a third, but did not change with subatmospheric pressures. A similar finding is reported in man (14).

Katz and co-workers have initiated a reinvestigation of cardiac dynamics in isolated heart and heart-lung preparations in a review by Landowne & Katz (15) of work and failure of the heart, in which are considered the work of the heart, its mechanical efficiency, adaptation to altered conditions, and the factors constituting the so-called cardiac reserve. Katz, Wise & Jochim (16) report on the study of the dynamics of heart-artificial lung and heart-lung preparations that the heart-lung preparations fail less quickly than isolated hearts, that heparinized blood is a more successful perfusate than defibrinated blood, and that change in the circulating blood volume is the most important regulatory device in the heart-lung preparation and, presumably, in intact animals. Failure of such preparations is indicated by (a) rise in venous pressure, or (b) failure of aortic pressure or cardiac output despite maintenance of venous pressure (17). Spontaneous improvement, possibly because of unexplained improvement in coronary circulation, becomes manifest in a fall in venous pressure and in a decrease in the size of the heart. They therefore reproduce experimentally "con-

gestive" failure where venous pressure rises while output and aortic pressure are maintained, and "forward" failure where a declining output is the first manifestation of failure (18).

Drury (19) supports the physiological attitude toward cardiac hypertrophy expressed by Landowne & Katz (15) with what appears to be an adequately controlled study of the hypertrophy appearing in the rabbit after establishment of a carotid-jugular anastomosis. In these animals the weight of the heart may double within three months after the arteriovenous anastomosis is made, yet where the anastomosis is tied off after hypertrophy has developed, the heart returns to its normal size within six to eight weeks. The report of Kohn & McEldowney (20) deals with the functional capacity of the damaged heart as demonstrated by the ability of victims of serious heart disease to survive and lead relatively normal lives.

Much of the same viewpoint finds expression in the reexamination of the necessity for complete bed rest in cardiovascular disease. Harrison (21) and Thomas & Harrison (22) studied the survival rate of rats suffering from myocardial trauma (burning the left ventricle) when mechanically restrained, when permitted to exercise at will, or when forced into strenuous exercise (swimming). The mortality was greatest in the restrained group (seven out of forty-nine survivors in this group against twenty-one out of forty-seven in the nonrestrained group). Forced strenuous exercise was not particularly harmful if it was not begun until forty-eight hours after the injury. The authors conclude that physical activity within the limit of tolerance may be more beneficial than complete rest. Levine (23) notes that the increased cardiac output during recumbency may largely cancel out the effect of other factors tending to reduce the work of the heart; while Dock (24) calls attention to the dangers of the Valsalva experiment when performed unknowingly, especially by patients suffering from myocardial infarction.

Starr (25) reviews the present status of the ballistocardiograph as a means of measuring cardiac output and Nickerson (26) gives details of the calculations involved in fitting cardiac output as computed from the amplitude of ballistocardiograph waves to estimations by the direct Fick method. Starr points out that the ballistocardiograph cannot yet give absolute values, but that it can detect alterations from the normal impact pattern. It may, moreover, be

used for repeated determinations in series, and the subject is spared the emotional stress of other procedures.

#### THE ELECTROCARDIOGRAM

*Basic theory.*—Ashman *et al.* (27) plot the distribution of net QRS and QRS-T potentials over the thorax using the common terminal lead of Wilson (without resistances) and find a spatial angle between the mean spatial QRS axis and the mean spatial QRS-T axis. This finding they consider to be in harmony with the general concept of the Einthoven triangle. Scherf (28) considers inversion or diminution in the amplitude of  $T_1$  and  $T_2$  after a long diastolic pause a sign of myocardial damage, the mechanism involving changes in the filling of the heart. Ashman *et al.* (29, 30) consider this and other manifestations associated with changes in rate as purely physiological, resulting from the influence of rate on the repolarization of various myocardial elements. Their further conclusion that the T wave reflects in direction and amplitude the difference in repolarization rates of elements in the septum, endocardium, etc., and even in different parts of single muscle fibers or between closely adjoining portions of small syncytial masses is more a reflection of the authors' general viewpoint than a consequence of the experiments they cite.

Wolferth and co-workers (31) have studied the effect of damage by potassium chloride or infarction on semidirect leads and conclude that in the chest leads negative RS-T segment changes cannot be produced at a cardiac surface by direct involvement of the fibers just under that surface, but must be secondary to pathological currents originating elsewhere in the myocardium. As far as the standard leads I, II, and III are concerned, Hoff & Nahum (32) show that occlusion of coronary arteries produces depression of the RS-T segment only when vessels supplying the right ventricle are occluded. Goldberger (33) suggests that the chest lead does not record preferentially from the region directly under the electrode, but from both ventricles, with the polarity of the effect determined by the orientation of the lead toward the endocardium or the epicardium. Groedel (34) reviews, from the standpoint of his previous work, the contribution of right and left ventricles to the electrocardiogram.

*Coronary circulation.*—Lorber & Greenberg (35) find that partial to total occlusion of the coronary sinus for three years does not

augment the coronary arterial bed, such as occurs acutely for a period of days to weeks after occlusion. The finding of Gregg, Shipley & Bidder (35a) of venous flow via the anterior cardiac veins of a magnitude that accounts for most of the blood hitherto thought to drain via the Thebesian channels, encounters objections from Lendrum *et al.* (36) who attempt to collect separately venous return via (a) the coronary sinus, (b) other right atrial drainage, (c) the right ventricle, (d) the left ventricle, and (e) the left atrium. Excised dog hearts were used, perfused with saline and 25 per cent dog serum, or with 100 per cent dog serum. Collections from the coronary sinus amounted to 36.4 per cent, the right atrium 24.5 per cent, the right ventricle 30.8 per cent, the left atrium 1.4 per cent, and the left ventricle 7.0 per cent as the mean of eight experiments.

Shipley & Gregg (37) have attempted without success to rule out the factor of increased metabolism in the augmentation of coronary flow that occurs when the sympathetic supply to the heart is stimulated, and suggest that the increased flow may be entirely the indirect result of an increased metabolism. Katz, Wise & Jochim (38) find in a study of the control of coronary flow in the denervated isolated heart and heart-lung preparation of the dog that the two most important mechanical factors influencing coronary flow are cardiac output and the systemic peripheral resistance (i.e., the more blood pumped out the more has to go through the coronaries, and the greater the extracoronary resistance the greater the coronary flow).

Bayley & LaDue (39), distinguishing between the myocardial changes due to occlusion of a coronary artery and those incidental to postoperative pericarditis (39), come to the conclusion that the first sign of deficient circulation is an elevation in the T wave in the direction of the future RS-T shift, i.e., in the opposite direction to the classical T wave change which develops later (40). This change may be produced by subtotal occlusion, and disappears within thirty minutes after restoration of the circulation. In total occlusion it may last for a few seconds only, and ushers in the RS-T displacement.

When an animal with an open thorax is ventilated with diminishing concentrations of oxygen and the intervals separating the excitation of several points on the ventricular surface are measured, no intraventricular block appears at concentrations as low



as 8 per cent, but in fact a slight diminution in interpunctal intervals appears (41). At 7 per cent oxygen and below, intraventricular block makes its appearance, associated with dilatation and failure. Consistently neither the electrocardiogram nor local leads show alterations in R wave amplitude at oxygen concentrations down to 8 per cent. With intact chests, animals begin to develop R wave changes at the comparatively safe level of 11 to 8 per cent oxygen. As anoxia develops the girth of the chest is noted to increase, and the reduction of R wave amplitude is proportional to the increase in girth, and can be reproduced by inflation of the chest. Changes in the T wave are not associated with chest inflation. Acute exposure to carbon monoxide causes a diminution in T wave height to diphasic or negative with a concentration of 70 per cent carboxyhemoglobin while at 80 per cent carboxyhemoglobin the T waves become acutely elevated (42). With chronic exposure inverted T waves appear in the second week, and elevation of RS-T and atrioventricular block with greater anoxemia (25 per cent carboxyhemoglobin for one hour or more). Murphy & Livezy (43) report a case of perforated gastric ulcer with hemorrhage and shock in which an electrocardiogram strongly suggestive of an infarct was found. Marked narrowing of the coronary arteries was found at postmortem examination suggesting that the myocardium did in fact become anoxic because of failure of its blood supply.

Goldbloom & Dumanis (44) consider the two-step exercise test of Masters of value as a test of cardiac function in cases where the electrocardiogram at rest is normal, and present a number of illustrative cases where positive signs, such as (a) depression of R-T greater than 0.5 mm. in any lead, (b) reversal of polarity of T, or (c) appearance of any significant arrhythmia, developed during exercise. In one instance the subject of the test died some time later from coronary occlusion. Pruitt, Barnes & Essex (45) produced extensive damage to the endocardium in dogs with little or no change in the RS-T segment, with inconstant T wave changes most apparent in 4R, and reduction of R and development of Q in 4R. These results add further evidence in favor of the concept that, in the standard leads particularly, the deeper layers of the myocardium contribute little if anything to the electrocardiogram. Rosenbaum *et al.* (46) describe two patients who after an anginal attack showed only minor T wave changes in the standard and unipolar extremity leads, but in precordial leads showed the

characteristic QRS and T changes of an anteroseptal infarct. Later extension of the lesion brought out the characteristic picture of acute myocardial infarction in the limb leads. The authors suggest that in other cases so-called "premonitory" signs may in reality represent anteroseptal infarction. Willius (47) has continued his historical outline of the development of knowledge relating to the coronary circulation and its diseases with an account of Harvey and the seventeenth century.

*Electrocardiographic changes in various conditions.*—The principal electrocardiographic changes brought out in patients with neurocirculatory asthenia by the tilt-table test are a decrease in amplitude or inversion of  $T_2$  and  $T_3$  (48). Similar alterations of amplitude and direction can be caused by vagotonia and sympathicotonia without in all cases a parallel effect on rate (49). The reversion of the electrocardiogram toward normal by the use of sympatholytic and vagolytic drugs serves to distinguish these changes from those due to coronary arterial disease.

Ball (50) reports that the S-T segment is always depressed in diphtheritic myocarditis, and that the changes are reversible and shifting and represent toxic rather than structural changes. The low amplitude of the T waves in congestive heart failure resulting from excessive desoxycorticosterone acetate therapy in the treatment of Addison's disease is undoubtedly a reflection of the low serum potassium; whether the failure develops for the same reason is not clear (51). Patients with mitral insufficiency show a significant percentage of tall P waves (3.0 mm. or more), broad P waves (0.12 secs.), and deeply notched P waves especially in leads II or III (52). One or two of the three were found in 62 per cent of patients as against 4 per cent in a control group. The angle of the electrical axis appeared to be of no value in characterizing the condition.

Rachmilewitz & Braun (53) report that, in sixteen patients with pronounced visceral manifestations characteristic of pellagra and responding promptly to niacine therapy, the principal electrocardiographic change was a flattening of the T wave which returned to normal following therapy. The authors raise the question of a direct metabolic effect of the avitaminosis which is reflected in the electrocardiogram. Comparing the electrocardiograms in forty-four young adults twenty-one to thirty-three years of age (24.8 yr. mean) with those of forty-four World War I veterans aged thirty-

nine to fifty-six (46 yr. mean) at rest and after exercise, Mazer & Reisinger (54) found that the only significant differences were to be detected after exercise: (a) a greater decrease in the R wave in young men, and (b) more frequent slight S-T depression in the older group (35 cases in 44 vs. 14 cases in 44), which might be a result of coronary artery disease. Their criteria for an abnormal response to exercise were: (a) S-T depression greater than 0.75, 1.5, and 0.75 mm. in leads I, II, and III respectively, and 1.75 mm. in CF4; (b) inversion of TI, II, or CF4; and (c) low voltage T in all limb leads.

The case is reported of sudden standstill of the heart of a seventy-four year old arteriosclerotic woman with total heart block and an acute upper respiratory infection. Epinephrine was given and the heart resumed beating after an arrest of 1.5 min. Twenty-four hours later ventricular tachycardia developed and terminated in ventricular fibrillation and eventual permanent arrest (55).

A noticeable feature of 118 electrocardiograms taken after artificial fever therapy in man was an increase in the value of  $K$  in Bazett's formula relating the deviation of the Q-T interval to the cycle length (56). Three of the group showed elevation of the S-T segment indicative of myocardial damage. Page (57), studying the circulatory responses to pressor drugs in experimental animals subjected to burns, observed similar changes in the heart volume and in the response of the peripheral vascular apparatus. He interprets these findings as indicating that parallel changes take place in the muscle of the heart and the blood vessels after burning. Barber (58) reviews the effects of direct and indirect trauma on the heart. Emetine is stated to produce minor changes only in the electrocardiogram, restricted in the main to depression of the T waves in all leads (59). The effect of amyl nitrite to cause an upward deviation in the inverted T wave of patients with hypertension or left ventricular enlargement is reproduced by deep inspiration (60), and is in part at least explainable on the basis of a rotation of the heart due to diminished size.

#### CARDIAC ARRHYTHMIAS

*Sinus and atrium.*—Pearson (61) describes the case of a hypertensive postmenopausal patient showing a persistent sinus bradycardia at a rate of 18 to 24 beats per min., with a normal P-R interval, in whom periods of asystole occurred, leading to syncope.

The pulse was not affected by atropine. Evans (62) employed CR<sub>1</sub> leads to permit better delineation of P waves and noted that in twenty-seven consecutive cases of paroxysmal atrial tachycardia, an atrioventricular dissociation (usually 2:1) could be detected in all. He concluded from this finding that atrial flutter and paroxysmal atrial tachycardia were in fact closely related, atrial flutter being in effect paroxysmal tachycardia at a slow rate (200 to 260 per min.) facilitating the detection of P waves and atrioventricular dissociation, while paroxysmal tachycardia represents the same condition at a much higher rate which prejudices recognition of hidden atrial waves and hinders discovery of atrioventricular dissociation. Decherd & Herrmann (63) come to the same conclusion from the consideration of patients in whom atrial flutter and fibrillation occur as well as paroxysmal atrial tachycardia. The finding of all three of these arrhythmias in the same individual suggested the possibility of a common mechanism, e.g., circus motion. This view was not, however, borne out in another series of studies by the same group. Measuring the amplitude of the P wave as recorded in electrocardiograms taken from three chest leads on horizontal, frontal, and sagittal planes, the electrical axis of the atria was calculated at 0.01 sec. intervals in each plane (64). Curves representing these consecutive atrial electrical axes were made and three-dimensional models constructed. Atrial flutter and fibrillation showed rotating axes compatible with circus motion, but paroxysmal atrial tachycardia did not (65). Howard (66) observed paroxysmal atrial tachycardia in the fourth day of life.

The relationship between vagal activity and atrial fibrillation in various clinical conditions is reviewed by Altschule (67). Recalling that intravenous injection of acetyl- $\beta$ -methylcholine in dogs produces both atrial fibrillation and A-V block, he finds a high correlation between the occurrence of a prolonged P-R interval and atrial fibrillation in patients with rheumatic fever, myocardial infarcts, and hyperthyroidism, and suggests that in these conditions the excessive vagal activity is in part responsible for the atrial fibrillation.

*Atrioventricular nodal conduction.*—Found through the employment of the tilt-table test in aviation medicine are four cases of exaggerated postural cardiovascular reflexes, in which a long P-R interval (0.4 sec.) is found when the subject is recumbent and a shorter P-R (0.2 sec.) when in the upright posture (68). Katz,

Langendorf & Cole (69) report a case showing premature interpolated ventricular extrasystoles followed by a P-R interval as long as 0.60 to 0.78 sec. The second P-R interval might also be prolonged, even to the point of block. Taking advantage of the observation that the P-R interval may be prolonged in rheumatic fever, Gubner, Szucs & Ungerleider (70) stimulated the carotid sinuses in patients with rheumatic fever and noted a more marked prolongation of the P-R interval than can be observed in normal individuals. The effect was maximal in the stage of acute carditis, and was augmented by premedication with prostigmine. They suggest such provocation of P-R delay as a test for the presence of the disease in cases which show no significant spontaneous prolongation. Numerous case reports of the Wolff-Parkinson-White syndrome have appeared (71 to 75) in one of which (73) electrocardiographic signs of myocardial infarction were noted (S-T<sub>1</sub>, 2, Q<sub>3</sub>, T<sub>3</sub>). Quinidine restored the normal rhythm in one case (74), while digitalis reestablished the abnormal rhythm. In another case (75) the QRS interval was abnormal but not prolonged, but became so after administration of cholinergic drugs. With atropine, QRS reverted to its previous condition, and retrograde P's developed, characteristic of an atrioventricular nodal rhythm. Butterworth & Poindexter (76) point out the similarity of the QRS complex in such cases to a fusion beat, i.e., a complex resulting from the double stimulation of the ventricles as by a normal beat and an ectopic stimulus, and suggest that the beats seen in this condition are in fact fusion beats. Ruskin & Decherd (77) calculated the consecutive electrical axis pattern in a single case of this syndrome and found it to be of the usual sinoatrial nodal type. The nature of the condition, and the suggestion that it depends upon the presence of accessory atrioventricular conduction tissue must be viewed in the light of knowledge of the normal atrioventricular conduction mechanism. A review of the present status of this problem by Glomset, Glomset & Birge (78) reveals how insecure the whole of the conventional concept may be. They find no evidence for a specialized atrioventricular conducting system in man, and claim that the atrioventricular bundle is represented in man by a tissue mass, the ridge fasciculus, structurally identical with other muscle fasciculi and having no special vascular supply or connective tissue sheath. This fasciculus, which has no left branch, has no muscular connections between it and the right atrium. They thus find no

support for the myogenic theory of atrioventricular conduction, and suggest a neurogenic mechanism (79). On the other hand, Robb & Kaylor (80) find the conventional pattern in the heart of the guinea pig, with a main bundle, right and left branches, and a septal branch. Kisch & Grishman (81) review the circumstances in which a transient intraventricular conduction defect may occur in man, listing myocardial infarction, carotid sinus pressure, quinidine and digitalis therapy, and tachycardia in coronary insufficiency as the principal conditions which may be responsible for its appearance.

Langendorf, Katz & Simon (82) report a case of reciprocal beating initiated by premature ventricular systoles. The case is presented of a fifty-four year old female with no detectable organic heart disease with a sinus rhythm interrupted by ventricular extrasystoles which are followed at a fixed interval by another premature complex of supraventricular origin. The constant interval between the two beats suggests to the authors the existence of a re-entry rhythm, with the point of re-entry in the atrioventricular node. A linkage via supernormality could equally well account for the phenomenon, without the necessity for invoking re-entry.

*Ventricular arrhythmias.*—In keeping with the recognition of the role of the sympathetic nervous system in the production of ventricular arrhythmias is the finding of Allen *et al.* (83) that vagal tonus is not an essential factor in the production of spontaneous cyclopropane arrhythmias in the cat, but that cardiac sympathectomy will abolish them. Evans, Osler & Krantz (84) report that cyclopropane sensitizes the heart of the rhesus monkey to epinephrine, but that this does not occur in propethylene anesthesia. Barnes & Ives (85) report sixteen instances in which ventricular arrhythmias developed during the first or upper second plane of trilene anesthesia. Eleven instances of bigeminy were noted, in six cases extrasystoles appeared from multiple foci, while in four instances these appeared at a rapid enough rate to constitute a tachycardia at from 130 to 200 beats per min. Simonson, Enzer & Goodman (86) diagnose coronary insufficiency from the electrocardiographic configuration of extrasystoles in a case where the supraventricular complexes were obscured by bundle-branch block. Boone (87) reports transient attacks of ventricular fibrillation in a case of hyperthyroidism. Marra (88) describes a case of paroxysmal tachycardia leading to syncope in a patient without demon-

strable heart disease. The attacks were prevented by daily doses of quinidine.

#### PHARMACOLOGY AND METABOLISM

McMichael & Sharpey-Schafer (89) have estimated the cardiac output by the direct Fick method in normal subjects and in patients with congestive heart failure before and after administration of therapeutic doses of digoxin intravenously, and report an invariable fall in right atrial pressure as measured by the indwelling catheter. In the normal group the cardiac output fell, while in the group with congestive failure the output rose. In the same group the simple mechanical lowering of venous pressure as by pooling behind tourniquets also resulted in an increase in output (although to a lesser degree than after digoxin). The authors therefore raise the question of how much of the effect of digitalization may be attributed to a peripheral action to reduce venous pressure and unload the heart to the point where it is no longer overdistended. Evidence of a direct influence on cardiac dynamics is however observed by Krop (90) using the isolated papillary muscle preparation of Cattell & Gold. The property of producing sustained augmentation of systolic force of mammalian cardiac muscle appears to be characteristic of the cardiac glycosides and is not shared by camphor, metrazol, coramine, and barium chloride. The xanthines (caffeine, theobromine, theophylline) are ineffective except in concentrations higher than are attainable therapeutically. Epinephrine has a marked hyperdynamic influence, the effect being immediate and short-lasting (10 to 20 min.) as compared with hours for digitalis. Therapeutically consistent doses of ephedrine may enhance the force of cardiac muscle, while higher concentrations depress it. Gold *et al.* (91) have employed preparations of digitoxin now commercially available as the method of choice in the digitalization of 1000 patients. Using their method of assay by the electrocardiographic method, they find digitoxin fully as effective by mouth as by vein, indicating that the material is fully absorbed by the gastrointestinal tract. One milligram of the product has the potency of 1 gm. of U. S. P. digitalis leaf, and the maintenance dose is close to 0.2 mg. daily. A dose of 1.2 mg. produces full digitalization in the average patient, and causes little or no gastrointestinal upset. It therefore becomes possible to give a full digitalizing dose at one time by mouth. Tandowski, Anderson &



Vandeventer (92) note that the electrocardiographic changes produced in man by ouabain, cedilanid, and digoxin are similar, but those of ouabain are maximal in ten minutes and fade significantly by two hours, while the effect of the other two is still maximum. Steldt, Anderson & Chen (93) compare the esters of strophanthin in cats. Blumenfeld & Loewi (94) note that low doses of digitalis have eventually a diastolic effect on the frog heart, as does increased calcium after a long latency. This similarity tends to support the old contention of a calcium-digitalis relationship. The eventual standstill of the heart after digitalis cannot, however, be prevented by a low concentration of calcium in the perfusate. Apter, Ashman & Hull (95) apply the concept of the ventricular gradient to the influence of ouabain on repolarization in the electrocardiogram. When digitoxigenin is injected into the head of a cross-circulation preparation isolated from the heart and lungs, slowing takes place independent of blood pressure changes and the carotid sinuses (96). This effect is not obtainable with digitoxin or strophanthin and presumably must be due to a direct action on the central nuclei of the vagi exerted by digitoxigenin alone.

Herrmann, Decherd & McKinley (97) found in a series of forty-four patients with overdigitalization that in seventeen the situation was diagnosed first by the electrocardiograph. There were twenty instances of paroxysmal tachycardia with atrioventricular block, six instances of isolated premature contractions, twelve instances of bigeminy and one of trigeminy, seven cases with atrioventricular block, one of sinoatrial block, two of nodal blocks, two of bradycardia, ten of atrial fibrillation, and one of flutter. Depression of the RS-T segment was seen in fifteen cases only. The use of digitalis in patients with failure and atrial fibrillation after myocardial infarction appears to favor the development of systemic emboli, possibly because the more vigorous heart beat it evokes facilitates the dislodgement of thrombi in a group of patients likely to have mural thrombi (98).

Tandowski (99) finds that Lanatoside-C reduces the frequency of recurrence of atrial tachycardia and flutter when it is injected intravenously in full digitalizing doses at the onset of the paroxysm. In seven out of eight cases this dose does not exceed 0.5 mg. daily. Thomas & Harrison (100) find that quinidine has very little influence upon mortality following experimental burns of the myocardium in the rat, and that there seems to be no need to adminis-

ter it routinely to prevent ventricular tachycardias in these circumstances. Reich (101) reports the successful use of massive doses of quinidine in a case of intractable ventricular tachycardia, employing 185 grains of the substance within a period of two and one-half days. He suggests the use of the electrocardiograph to control dosage, with an allowance of a 25 per cent increase in the duration of QRS as the permitted limit.

Enikeeva (102) states that in puppies less than forty-five days old the vagus centers show neither tonic nor reflex activity, but nevertheless the heart responds to the injection of large doses of epinephrine by slowing. Sympathectomy gives a slow heart uninfluenced by epinephrine. The suggestion is made that epinephrine acts centrally to inhibit sympathetic tone, somewhat in the manner of a Wedensky inhibition: "Peripheral volleys to the heart are cut off through over-excitation of the sympathetic neurones." The influence of thyroxine on the response of the heart to epinephrine is confirmed by Raab, who shows that the concentration of epinephrine required to kill the rat heart is less in thyroxine-treated and greater in thiouracil-treated animals (103).

Moses (104) finds that moderate hyperthyroidism depletes cardiac glycogen proportionally to the increase in heart rate, but not to the increase in metabolism. Tachycardia of an equal degree, produced in other ways (atropine, chilling), depletes heart glycogen to an equal degree. Primary anemia reduces glycogen proportionally to the decline in hemoglobin. The suggestion is offered that the depletion in glycogen is caused by a relative ischemia due to increased heart rate.

Raab (105) has continued to investigate the distribution and concentration in the blood and heart muscle of a catechol compound presumably of adrenosympathetic origin. The material is found in excessive amounts in the blood and heart muscle of patients dying with uremia, and the findings parallel roughly the electrocardiographic changes (anoxic) and clinical signs of failure. The sera of uremic patients is found to be toxic to the frog heart, which responds in an identical manner to poisoning by known catechols and by phenol. These compounds are therefore considered to contribute to the death of uremic patients. Wendkos (106) employs ergotamine to uncover the hyperactivity of the vagus noted in the acute stage of rheumatic fever, as a provocative test in those patients in which the spontaneous vagotonia is

masked by sympathetic activity. [See also Gubner *et al.* (70).]

Allen, Murphy & Meek (107) find that the heart of the decerebrate dog is not slowed by morphine although carotid sinus stimulation is effective; nor is the pulse slowed in crossed circulation experiments in which the blood reaches only the medulla. They conclude that morphine bradycardia results in part at least from the blocking of cortical impulses which normally inhibit medullary vagal activity. Hoff, Humm & Winkler (108) extend the work of Howeli to the mammal in demonstrating that the influence of the vagus or of acetyl- $\beta$ -methylcholine chloride on the dog's heart is potentiated by increase in serum potassium. Studying the slowing of the heart that occurs when posterior pituitary extract is injected into the dog, Sawyer & Ettinger (109) find that this effect and the electrocardiographic changes disappear after total denervation of the heart. In one experiment slowing occurred without rise in blood pressure, leading to the conclusion that the carotid sinus mechanism is not the sole factor involved.

The mechanism for inactivation of epinephrine has been studied by Bernheim & Bernheim (110) who find that the ventricle of the rat, rabbit, guinea pig, and, to a lesser degree, the dog and cat can inactivate tyramine by oxidation of both the amino and carboxyl groups. Cocaine and ephedrine inhibit deamination but not oxidation. The authors ask whether this oxidase is involved in the normal inactivation of epinephrine or in the sensitization to epinephrine that occurs after denervation. One mg. of dog heart is found to inactivate 6  $\mu$ g. of tyramine per minute, which is much slower than the inactivation of acetylcholine by esterase. The same authors report that incubation of the rat heart for 5 to 20 min. at 37° C. before slicing depresses respiration but does not interfere with the oxidation of succinic, lactic, and pyruvic acids, indicating that the cytochrome-cytochrome oxidase system, coenzyme I, and thiamine pyrophosphate are still functioning. The absence of potassium, calcium, or magnesium or the presence of 0.03M chloral hydrate, or avertin has a similar effect. Anaerobiosis disturbs metabolism somewhere between the hexose phosphates and lactic and pyruvic acids (111). Heart glycogen increases in alloxan-treated rats (0.442 to 0.854 per cent) while liver and muscle glycogen decrease (112). Treatment of an animal with desoxycorticosterone acetate does not impair the ability of the heart to take up potassium when it is injected in glucose-containing solutions (113).

One of the veratrine alkaloids, protoveratrine, is observed to be ten times as toxic as veratridine in mice and to bring about positive improvement in hypodynamic hearts in a calcium-poor perfusate. The heart is slowed by a combination of central and reflex stimulation of the vagi (114). It is claimed that magnesium sulfate (0.5 cc. of a 20 per cent solution) prevents fibrillation that otherwise follows injection of mercurial diuretics in dogs (115). Electrocardiograms taken during fatal intravenous injections of mercurial diuretics in man show ventricular fibrillation to be the cause of death (116). A cardiotoxic factor has been found in the culture fluid of hemolytic streptococci, which is effective only after a second injection of the material (117). The lack of action after the first appears to be due to the release of an "inhibitor" which is exhausted by the first injection (118). Crismon (119) has studied the effect of hypothermia on the heart in the white rat and has found a linear relation between heart rate and body temperature and also between atrioventricular conduction rate and body temperature, with a  $Q_{10}$  of 2.14. In heart-lung preparations of the dog, tetraethyl ammonium bromide is effective in minimal concentrations of 1:70,000 to 1:100,000 augmenting the beat of hypodynamic hearts (120). In the intact cat slow intraperitoneal or intravenous injection of 30 mg. per kg. gave a progressive bradycardia unaffected by vagotomy and associated with increase in the T wave, displacement of the S-T segment, and ventricular fibrillation.

The introduction of thiouracil makes possible the treatment of angina pectoris and congestive heart failure by the reduction of basal metabolism without surgical ablation of the thyroid and a favorable report covering the successful treatment of seven out of ten cases of angina pectoris has appeared (121).

#### CONGENITAL ABNORMALITIES

The successful surgical treatment of malformations of the heart in which there is inadequate pulmonary circulation because of pulmonary atresia or stenosis by anastomosis of a systemic artery (subclavian or innominate) with one of the pulmonary arteries (122) emphasizes the need for thorough knowledge of the disturbed anatomy and physiology of the various conditions. Obviously the improvement can be sought only in those cases where the primary defect is in the pulmonary circulation, and the treatment will be of no avail in such conditions as transposition of the great vessels,

Eisenmenger's complex, and aortic atresia. Burrett & White (123) describe the case of a forty-three year old woman with a large interatrial septal defect who presented symptoms of pain radiating to the neck and arms, cyanosis, left-sided cardiac enlargement, right axis deviation, and a precordial systolic murmur. The cause of the murmur appears to be questionable inasmuch as a pre-systolic murmur might be expected were the defect itself the source of the sound. Glendy, Glendy & White (124) describe a case of *cor biatriatum triloculare*, with an excellent plate. Knop & Bennett (125) add a new case to a series of fifty-five instances of anomaly of the coronary artery with the description of the heart of an infant dying suddenly on the fifth day of life. There was congenital absence of the left coronary artery, with the atrophic left ventricle supplied by an inadequate branch of the right artery. In none of the other cases collected was the anomaly the apparent cause of death. The most common anomalies were the presence of accessory orifices (28 cases) and aplasia or absence of the right coronary (11 cases).

#### HEART SOUNDS

In cases of thoracic defects, it is reported (126) that heart sounds are louder, part of the high frequency vibrations are absent, and that sounds of low amplitude of whatever frequency, become distinct. The question is raised whether the high frequency vibrations are not due to resonance effects from the ribs. Garb (127) reports on the relationship of blood viscosity to the intensity of heart murmurs that the murmur decreases with increasing viscosity and increases as the blood becomes less viscous. Maximum amplitude is attained at hemoglobin concentration of 70 per cent. Levine & Likoff (128) note that murmurs may be detected by applying the stethoscope to such regions as the olecranon or skull, and conclude, therefore, that they are not transmitted by the blood stream. Loudness is an important characteristic, a grade 3 or louder murmur never being found in normal individuals. Exercise produces systolic murmurs in normal individuals and the intensification of a systolic murmur by exercise has no pathological significance. Luisada (129) recorded the apparent diastolic rumble or Austin Flint murmur heard in twenty-seven patients with aortic regurgitation and, on analysis of the records, finds that the sound represents in reality one of the following: (a) additional diastolic

sounds, mainly the third heart sound and the atrial sound, (b) a split first sound, or (c) a crescendo type of first sound. None of these patients had, therefore, a true Austin Flint murmur. Sodeman (130) reviews the classification and characteristics of the systolic murmur, Groedel & Kisch (131) report five cases of pre-systolic murmurs in the absence of atrial systole, and Hecht & Myers (132) describe loud, clear, clicking atrial sounds heard in atrial flutter. Luisada reviews briefly the application of phonocardiography to normal and abnormal heart sounds (133).

#### TECHNIQUE AND MISCELLANEOUS

Leads taken from the right arm or left leg and the right side of the sternum in the third interspace give good atrial records and obviate the necessity for oesophageal leads (134). An electronic switch operating at a frequency of 2500 c.p.s. is used by Dawson & Jones (135) to record heart sounds and the electrocardiogram apparently simultaneously with a single-beam cathode ray tube. Etheridge & Stolar (136) have designed a compact switch for use as a lead selector for the multiple leads that have gained currency.

Resting pulse rates in college and high school students show great variability and single determinations are unreliable (137). With strenuous exercise maximum pulse rates are attained in all subjects, whether fit or nonfit, and in consequence individuals with the slowest resting pulse rates will show the greatest increase, while with moderate exercise the fit group will show the least increase in pulse rate (138).

Amann & Schaefer (139) have recorded action currents in afferent fibers from the heart in cats under chlorolose-urethane narcosis and detected no centripetal impulses in the vagus itself unless the blood pressure was lowered by veratrine or mistletoe. The aortic nerve yielded impulses synchronous with the pulse beginning with the ejection phase. After veratrine the impulses appeared in diastole also, and after arrest of the heart they were continuous. Only a few of the direct fibers from heart to vagi were afferents, but these showed bursts of impulses synchronous with atrial and ventricular systoles.

The heart of natives living at altitudes of 10,000 to 15,000 feet has an average transverse diameter 11.5 per cent and a frontal area 16.3 per cent greater than whites at low altitudes (140). In shock produced by bilateral venous occlusion in the hind legs of

the dog the heart size as determined by x-ray fell to 65 per cent of the control valve in the first quarter of the postoperative survival time (141), and thereafter fell very little. Heart rate was not an important factor in the change in size, the diminution in size being the same in groups showing the least and the greatest change in rate. Studying the position of the heart as outlined by intravenous injection of radio-opaque materials, Taylor & McGovern (142) conclude that the right ventricle does not occupy more than about one-half of the cardiac silhouette. Friedberg & Lewis (143) review the normal standards of size, rate, output, and the electrocardiogram in old age.

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## SHOCK

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The war years have witnessed radical changes in our concepts of shock. The prewar literature was supersaturated with hypotheses and unitarian explanations of shock, and the experimental studies largely revolved around efforts to prove or disprove one of the current theories. Dominant among these was the concept that the fundamental disorder in shock consisted of generalized capillary leakage. The origin and development of this theory is, in itself, an interesting study. In retrospect, it appears that its wide acceptance resulted not from the presentation of convincing experimental evidence, but from frequent repetition by several authorities. When at the beginning of World War II various groups were enlisted in the study of shock, a different spirit emerged. The theories were largely by-passed. Groups working in various laboratories and clinics approached the problem more impartially and some set about making a systematic study of the bodily changes in shock produced by several different types of injury. The results of new facts brought out by these studies have settled several controversial issues. They have also demonstrated that there are many causes of shock and that several different mechanisms may be concerned in its production. Prior to the war there was also a great paucity of physiological data on human cases of shock. Well-planned studies in several clinics have corrected this situation and in great part the results of experimental studies on animals have been confirmed on humans.

In spite of the fact that a good deal of war research on shock is as yet unpublished, over two thousand papers on this topic have appeared during the war years. Of these, at least eight hundred can be classed as experimental. It is obviously neither practicable nor desirable to attempt to cover all these. Although a review on shock has not previously appeared in the *Annual Review of Physiology* or the *Annual Review of Biochemistry*, references to the literature preceding the war have been omitted. A summary of the latter will be found in the monumental review by Harkins (1), in Blalock's Monograph published in 1940 (2), and in the challenging

survey of the problem made by Wiggers in 1942 (3). For references to recent literature the *Bulletin of War Medicine* deserves special attention because of the critical judgment displayed in abstracts prepared by some of our British colleagues.

*Criteria of shock.*—One of the greatest difficulties in evaluating or comparing the results of various experimental studies on shock arises from the fact that in many instances the evidence as to whether or not the animals were in shock is either inadequate or totally lacking. Clinically, shock is recognized and defined by certain signs and symptoms. The problem, experimentally, is to determine the bodily changes which are associated with and give rise to the clinical picture. It is apparent that one cannot hope to obtain reliable information about the physiological disturbances in shock without reproducing the syndrome, and the only valid proof of having done so lies in the appearance of the signs that are the accepted clinical criteria of shock. With altogether too few exceptions the term "shock" has been applied where the only evidence given of its existence was a reduced blood pressure and a fatal outcome. By itself, a low blood pressure is not a reliable index of shock and death may result from many other causes. Therefore it is sometimes questionable that so-called "shock experiments" have anything to do with shock. Also there seems to be a tendency in some quarters to abandon the accepted clinical definition of shock and to restrict the application of the term to instances in which remedial measures are ineffective. For example, it has been suggested by one investigator that "shock, in a highly restricted sense, can perhaps not be said to exist until a stage of irreversible circulatory failure has developed" (3). Is one to infer from this that successful treatment of a patient in shock means that the patient was not in shock? A clinician would scarcely concede this point.

The great majority of investigations of shock have been of such character that they have necessitated the use of a general anesthetic. Under these circumstances, it is manifestly impossible to reproduce all the clinical signs of shock, because many of these are modified or masked by the anesthesia. An equally serious objection is that the anesthesia also modifies the compensatory mechanisms operating after injury. Therefore the bodily changes ensuing from injury will be somewhat different both qualitatively and quantitatively and follow a different course than that seen in the unanesthetized animal. This has admittedly been a serious problem to many

investigators. Wiggers (3), however, takes the unique view that the use of anesthesia has experimental advantages in that it eliminates visual, auditory, and psychic influences. If, as stated above, one sets out to investigate the relation between the clinical signs and their underlying causes, the factor of anesthesia can only be regarded as an added complication, the influence of which must be ruled out in the final evaluation of the results of injury. A further consideration not fully appreciated is that whereas it may be possible to establish a uniform degree of narcosis in the normal animal before injury, it does not follow that the depth remains the same afterwards. Indeed as shock develops the narcosis becomes deeper (4). In this laboratory we selected a form of injury (5) with which the use of general anesthesia could be limited to the short period during which the injury was inflicted (6). We were then able, during the succeeding hours, to observe the development of the clinical picture associated with various stages and degrees of shock. Inasmuch as the symptoms and signs are useful indications of functional derangement, they should be accorded more emphasis and careful study than they have been given generally in experimental studies on shock. It now seems clear that the recognition of clinical signs as a reference point, or common denominator, in experiments would have prevented the appearance of much contradictory evidence as well as the controversial state of several aspects of the problem.

The great variety of methods and substances used in producing shock experimentally also makes it exceedingly difficult to evaluate and reconcile the results of different workers. Here also, the systematic study of the clinical picture would be helpful in giving clues as to differences in the nature and patterns of the functional disturbances resulting from each type of insult. Special features of the physiological changes, such as hemoconcentration, which are determined by the character of the injury have not infrequently been taken as inherent characteristics of shock.

*Methods.*—A large variety of methods has been employed for producing traumatic shock experimentally. These include the use of a tourniquet on one or more extremities (7 to 10), tourniquet on isolated muscle groups (11, 12), crush (13 to 17), compression (19), muscle trauma by contusion with light hammer blows (5, 6, 10, 20, 21), Noble-Collip drum (22, 23), gun shot wounds (6, 17, 18), intestinal trauma (24), strangulation of intestinal loops (25), freez-



ing (26, 27), and burns. The so-called "gravity shock" (28, 29) in which there is no reduction in blood volume has also been employed and studied by several workers. I have not encountered published reports on tamponade, although this would seem to be worthy of investigation in view of the similarity in circulatory impairment to myocardial failure (30).

Hemorrhage has been widely employed both in large and small animals, and an increasing number of these studies has been done without the complicating factor of anesthesia.

The production of shock by stimulation of afferent nerves has also been tried (31, 32). Prolonged stimulation of the aortic depressors leads to fatal outcome in rabbits. Stimulation of somatic afferent nerves, unless combined with hemorrhage, has not so far been shown to cause shock (31, 32, 33).

The studies of the relation of toxic agents to shock or shock-like states include experiments with histamine (34, 35), chymotrypsin (36), continuous injection of large doses of epinephrine (37, 38), callicrein (39), peptone (40), hydatid fluid (41), bacterial toxins (11, 12), muscle extracts (11, 12, 42, 43, 44), lymph from traumatized areas (45), and blood from animals in shock (46, 47). Recent experiments with intraperitoneal implantation of muscle indicate that the toxic factor in this instance seems to be mainly bacterial in origin (48, 49). The motive behind most of these experimental studies has been to ferret out the toxic factors in shock.

*Standard procedures for producing shock.*—The crying need for procedures which invariably produce shock was well recognized at the beginning of the war. Even as late as 1942, Wiggers (3) wrote "the efforts to devise a standard procedure that will unfailingly produce shock seems as hopeless today as in 1903." This matter has been given a good deal of attention in studies on traumatic shock, and recent investigators have, for the most part, defined the experimental conditions faithfully and tried to determine quantitatively the relation between the severity of the injury and the survival time as well as the mortality rate. However, the results obtained by different workers using, for example, limb tourniquet or crush reveal only fair agreement. Injury by muscle contusion (5) which we selected because it could be carried out under a brief period of anesthesia can, after some experience, be employed by the same person, from day to day, with a fair degree of uniformity in the outcome (6). But it is our experience that even with careful

imitation of all experimental details, another individual cannot duplicate the results simply by applying the same number of blows. The number must be adjusted to the force of the strokes and their distribution, and these are matters of "feel" that one cannot well describe. Examination of the results of trauma experiments, regardless of the type, shows a considerable spread in survival time, and although the mortality rates can be made to fall near 100 per cent, few workers, I think, would be willing to claim that exceptions do not occur and that the procedure unfailingly produces shock. As a rule, proof of the benefits of a therapeutic measure by means of mortality rate, therefore, requires the use of a large series of animals.

Offhand, the production of shock by hemorrhage would seem to present a much simpler challenge. This however is also fraught with difficulties, mainly because of individual variations (*a*) in the normal blood volume per unit body weight, and (*b*) in the compensatory reactions to hemorrhage. Hence, withdrawal of blood up to some fixed percentage of the body weight, or even withdrawal of a fixed fraction of the measured blood volume in a single massive hemorrhage, does not invariably result in death in shock. With either method, a considerable proportion of animals either die in acute circulatory failure at the time of bleeding, or recover uneventfully without displaying the clinical picture of shock (50).

In attempting to standardize hemorrhagic shock, most investigators have resorted to various schemes of repeated or graded hemorrhages, in some of which an arbitrary degree and duration of hypotension is utilized as a guide to the amount bled (52, 53, 54). For testing the replacement value of blood substitutes in dogs, Lawson (55, 56) has devised an interesting method which consists of bleeding at a constant rate (2 cc. per kg. per 3 min.) until the blood pressure approaches a terminal plateau. His evidence shows that the blood collected up to this point is short of the bleeding volume by a constant amount.

In unanesthetized dogs the range of reduction in blood volume (by a single mass hemorrhage) that produces the desired result, namely, the appearance of clinical signs of shock and death, is rather narrow (50). The residual blood volume must range from 52 to 57 cc. per kg. body weight (51). This represents a reduction of about 40 to 48 per cent of the normal volume. However, the amount of blood per kilogram body weight that must be with-

drawn to produce this reduction may vary widely in different dogs (50). A simple and rapid procedure for bringing the blood volume into the shock range has been devised by Walcott (57, 58). The unanesthetized dog is exsanguinated from the femoral artery within a few minutes, and one-fourth of the blood collected is then immediately returned to the circulation. Without exception, all animals so treated and kept in the usual supine position on an animal board die in shock in about four hours. The survival time is surprisingly constant.

*Physiological and biochemical changes in shock.*—These are so numerous and variable depending on the type of injury and other experimental conditions (e.g., anesthesia) that the attempts, in the past, to evaluate the severity of shock or its various stages by any single measurement have not been notably successful (59). In recent years, more comprehensive studies of the over-all physiological and biochemical changes have been undertaken (6, 11, 12, 28, 59, 60, 61). The addition of new and improved techniques, such as the use of radioactive tracers, improved methods of measuring blood volume, optical recording of arterial and venous pressures, cardiac output determinations in man, renal clearance methods, and chemical analyses for various blood and tissue constituents, have greatly increased the data obtained in both experimental and clinical studies.

The data summarized in the following table indicate the general magnitude and range (6, 71) of some of the circulatory, respiratory, and blood changes found in dogs at such time after hemorrhage or trauma when they displayed unmistakable signs of severe shock, e.g., extremities cold, skin bloodless, peripheral veins collapsed, oral mucous membranes dry and pale, thirst, lack of sensitivity to pain, and central nervous depression bordering on coma. These average values were derived from a long series of experiments in which the reduction in blood volume was approximately the same (40 to 50 per cent). It should be noted also that both the control and experimental observations were made when the animals were unanesthetized.

Several facts not revealed by the table are important in the interpretation of the data. Most of the changes shown occur progressively, but this is not true of the blood volume. The reduction in the latter occurs at the time of injury. Thereafter, not only the blood volume but the hematocrit and plasma protein values remain

TABLE I

SUMMARY OF CHANGES OBSERVED IN SEVERE SHOCK RESULTING FROM MUSCLE TRAUMA OR HEMORRHAGE IN DOGS. RANGE OF BLOOD VOLUME REDUCTION 40 TO 50 PER CENT

	Control	Shock Hemorrhage or Trauma
Pulmonary ventilation, liters per min.....	2-8	3-17
Oxygen consumption, cc. per min.....	80-125	35-60
A-V oxygen difference, vols. per cent.....	3-7	14-20
Cardiac output, liters per min. (Fick).....	2.0-3.0	0.3-0.5
Heart rate, per min.....	60-90	180-250
Stroke volume, cc. per beat.....	25-35	1.5-2.5
Mean blood pressure mm. Hg.....	100-120	40-90
<i>Arterial blood:</i>		
pH.....	7.35-7.40	6.90-7.20
pCO <sub>2</sub> , mm. Hg.....	35-40	10-20
CO <sub>2</sub> , mM per l. H <sub>2</sub> O.....	20-24	3-8
CO <sub>2</sub> vol. per cent.....	44-53	6.6-17.6
Cl, m. eq. per l. H <sub>2</sub> O.....	113	No change
Lactate, m.eq. per l. H <sub>2</sub> O.....	1-3	10-18
Phosphate, m.eq. per l. H <sub>2</sub> O.....	2-3	5-10
Pyruvate, m.eq. per l. H <sub>2</sub> O.....	0.1	0.4
Sulfate, m.eq. per l. H <sub>2</sub> O.....	2-3	3-4
Sodium, m.eq. per l. H <sub>2</sub> O.....	156	No change
Potassium, m.eq. per l. H <sub>2</sub> O.....	4	No change until last hour, then rise to 10-15
Calcium, m.eq. per l. H <sub>2</sub> O.....	5-6	No change
Magnesium, m.eq. per l. H <sub>2</sub> O.....	1.7	3.4
Total cations, m.eq. per l. H <sub>2</sub> O.....	160-170	No change
Total base determination, m.eq. per l. H <sub>2</sub> O..	160-170	No change
B-C* (average).....	+1.6	-1.0
B-A† (average).....	11.0	14.6
NPN mg. per cent.....	28	59
		(in anuria)

\* Sum of individual cations.

† Sum of individual anions.

essentially unchanged until the animal succumbs. Hence, contrary to earlier concepts, the gradual failure in the circulation, at least in these two forms of shock, cannot be ascribed to a gradual decrease in blood volume (62). The progressive character of shock is

dependent upon the changes in cardiac output. After the immediate large fall in cardiac output which occurs at the time of injury and reduction in blood volume, there is a steady decline to the very low values (10 per cent of the control) shown in the table (63). With the gradual fall in cardiac output, there are, as one might expect, progressive and eventually profound changes in the oxygen consumption, arterio-venous oxygen difference, and ventilation. It should be emphasized that no change occurs in the arterial oxygen saturation.<sup>1</sup> These findings and the clinical evidence of slowed blood flow disclose a condition of stagnant anoxia. A survey of the major blood changes shows the development of severe acidosis. The pH falls while lactate, phosphate, and pyruvate rise. Several other workers have investigated these changes in pH (28, 60, 61), lactate (28, 59, 61, 64, 65), and phosphate (28, 61, 66, 67) in various types of experimental and clinical shock. The rise in amino acid nitrogen has been studied especially in relation to the role of the liver in shock (64, 68, 69, 70). Also blood glucose changes in shock have been investigated recently (65, 68, 69). The arterial carbon dioxide is greatly reduced. This occurs partly because the fixed acids combine with the base of the bicarbonate, setting free carbon dioxide, and partly because  $p\text{CO}_2$  is reduced as a result of the increased ventilation (71). All these changes in blood chemistry are interrelated and if considered together they provide reliable objective criteria for evaluating the degree and severity of shock (6, 71) and for testing quantitatively the effectiveness of various therapeutic measures (72) in combating the metabolic disturbances induced by the tissue hypoxia. Under appropriate experimental conditions the arterial carbon dioxide (73) or the venous oxygen (74) may alone serve as a fairly reliable index of the severity of shock.

Among the electrolytes, a small increase is found in the sulphate and magnesium levels. The potassium undergoes little (75) or no change (76) until shortly before death when it rises sharply and may approach a level in the plasma which is toxic to the heart (14 mM per l.). The same is true in tourniquet shock (77). In brief, recent evidence fails to support earlier claims that shock can be attributed to a rise in the blood potassium level. This is clearly a terminal event, for in dogs that have recovered from trauma no

<sup>1</sup> Instances of decreased arterial oxygen saturation in shock are readily explained either by depression of respiration by narcosis or by special circumstances that interfere with pulmonary functions.

change was found in the blood potassium level during the period when according to clinical signs and the blood changes mentioned above the animals were in severe shock (76). The total base is essentially unchanged. The B-A, however, is slightly raised, suggesting that there is a small increase not accounted for, in the amount of some fixed acid (71). Studies on four clinical cases of shock (61) reveal changes of the same magnitude in the B-A.

The urinary secretion is either scant or, in severe cases, totally absent. One result of this is a rise in the nonprotein nitrogen (see table). Renal clearance studies on dogs in shock (78, 79) and on clinical cases of shock (60, 61, 81) show that the renal blood flow and glomerular filtration are severely depressed. The effect on clearance measurements of temporary occlusion of the renal artery indicates that clearance studies in shock must be interpreted with caution (80). From the clearance studies and simultaneous measurements of cardiac output it appears that the restriction of renal blood flow by vasoconstriction is an important compensatory mechanism for maintaining blood pressure and a relatively larger blood flow through other regions of the body (81). These and other clinical studies (82, 83, 84, 85) contain valuable information on the effects of therapeutic measures on the circulatory dynamics. Interesting studies on cardiac output have been made in acute circulatory collapse produced in normal subjects by tilting, by venesection, or by pooling of blood in the extremities (87, 88, 89, 90). The evidence shows that fainting cannot be explained by decreased cardiac output; rather, it is caused by peripheral vasodilatation in the muscles. It is conceivable that a similar mechanism may operate in the final stages of traumatic or hemorrhagic shock. Attention may also be called here to recent work on the Fick (91, 92) and other (93, 94) methods for measuring cardiac output. Questions have been raised in regard to the accuracy of the Fick method, but it is improbable that the errors are sufficient to affect significantly the general conclusions concerning changes in cardiac output in shock.

*Blood volume.*—In hemorrhage and various types of trauma a large reduction in blood volume is the initial step in the train of events leading to shock (6). The relation between reduction in volume and the incidence of shock was shown many years ago by Keith and others, but the magnitude of the changes involved was not generally accepted until recently, because the blood volume

methods were held to be unreliable, especially for measuring volume in shock (20, 95, 96, 97). There were several reasons for this view: (a) reports of inconsistent results as a consequence of using the methods without due regard for the technical and physiological precautions which are necessary (6, 98); (b) controversies regarding the interpretation of the time-concentration curves and the mixing of the test substances used for measuring plasma volumes; (c) earlier discrepancies between total blood volume values estimated with methods for measuring red cell volume (carbon monoxide, radio-iron) and those estimated with methods that measure plasma volume (e.g., dye methods); (d) the belief that the slowed blood flow in shock would interfere with mixing and especially that increased capillary leakage in shock would vitiate the determination. Most of these difficulties have been cleared away by recent critical studies of the methods and by the overwhelming evidence against the concept of "generalized capillary leakage."

The dye method (T-1824) has been the one most used for measuring blood volume. In the usual interpretation of the dye curve (99) it is assumed that the rate of loss of dye during the first few minutes after the injection (mixing period) is given by the subsequent slope of the curve (disappearance). Strong support for this view has been supplied recently by the demonstration that simultaneous measurements of plasma volume with T-1824, bovine albumin, bovine globulin, and the polysaccharide SIII yield the same value (100). This and other evidence (101) disprove the contention that a considerable fraction of the dye escapes during the mixing period; in other words, that the early rapid phase of the dye curve represents loss of dye and not mixing (102). Errors in measuring plasma volume arising from unexplained alterations in the dye curves have been reported to occur after giving morphine or hyascine (103).

Simultaneous measurements of blood volume with dye and an improved carbon monoxide method (6, 98, 101) agree almost within the experimental error of the methods. According to this evidence, the unequal distribution of erythrocytes in the circulation is not as great as hitherto believed. It should be noted that disregard for the carbon monoxide content of control blood was found to be one source of considerable error in earlier work with the carbon monoxide method. On the average, a similar agreement between dye and carbon monoxide measurements has been found



by Hopper, Winkler & Elkington (104, 105). For rather inadequate reasons these authors appear to doubt that either method measures the absolute volume. Comparative studies with radio-iron, carbon dioxide, and T-1824 will presumably give a final answer to the problem. However, in the opinion of the author it does not appear that the unequal distribution of erythrocytes in the circulation is sufficient to interfere seriously with a correct appraisal of total blood volume with the dye method (98).

The dye method (T-1824) gives consistent and reproducible results in dogs in traumatic shock, provided "fair" samples of the circulating blood are obtained, preferably from an artery. Peripheral venous samples from dogs in profound shock do not infrequently give bizarre results (62). Trauma usually causes hemolysis, but the level of hemolysis changes only gradually. Therefore, it does not introduce significant error in the dye determination provided the blood is collected without causing additional hemolysis in the samples.

The dye disappearance rate in dogs is often greater immediately after hemorrhage or muscle trauma. This is not regarded as evidence of actual increase in general capillary permeability (62). Redistribution of the blood after a loss in volume may reduce the fraction of blood flowing through regions of low capillary permeability (muscles) and leave a larger fraction passing through internal organs (liver) where the leakage is normally high. At any rate, extrapolation of the dye curves corrects the determination of plasma volume for these differences in disappearance rates.

The first series of our studies on blood volume in traumatic shock in dogs indicated that trauma sufficiently severe to produce a clinical picture of shock caused a reduction of at least 30 per cent in the plasma volume. In animals that succumbed the reduction was generally 40 per cent or more. There was also evidence that survival time was inversely related to the degree of reduction in volume. Later studies have demonstrated that the metabolic disturbances make their appearance when the blood volume reduction exceeds 20 per cent (63). Statistical treatment of the data from experiments accumulated over a period of three years reveals a significant difference in the relation of blood volume reduction to mortality rates in traumatic and hemorrhagic shock (51). In a simple hemorrhage, the residual blood volume at L. H. 50 (50 per cent mortality) was found to be 57 cc. per kilogram whereas in traumatic shock it was 71 cc. per kilogram. These results show that

reduction in blood volume is not the sole cause of death in shock after trauma.

Several investigators have studied the changes in blood volume in clinical shock (60, 106 to 109). Systematic study of the dye curves (these must be corrected for fluid shifts in order to estimate the disappearance rate) fails to show that dye escapes more rapidly in patients in shock than it does normally (106, 107). An increased disappearance rate is found only in cases of burns and abdominal injuries with peritonitis. The average mixing time as estimated from the dye curves is nine minutes in normal subjects, fifteen minutes in cases of shock from hemorrhage or skeletal trauma, and seven minutes in patients with similar injuries but not in shock (98, 107). In man as in the dog, shock from hemorrhage, trauma, or both is associated with a reduction of 30 to 40 per cent in blood volume. In injured patients, judged to be in shock on clinical evidence, the volume was, with few exceptions, at or below 55 cc. per kg., or 2000 cc. per sq. m. body surface (108) whereas the average for normal subjects is about 83 cc. per kg. or 3100 cc. per sq. m. In the average patient displaying the clinical picture of severe shock after hemorrhage or skeletal trauma, it may therefore be assumed that approximately two liters of blood have been lost. This is in agreement with practical experience with the amount of blood required for resuscitation (110). It should be noted, however, that other forms of shock may not involve reduction in blood volume (e.g., myocardial failure). A simplified method of determining blood volume, suitable for clinical use, has been described (98).

*Generalized capillary leakage versus local fluid loss.*—The efforts of many investigators have been directed toward this problem. Recent evidence, direct and indirect, fully supports the earlier contention of Blalock (2), Phemister (31, 32), and others that in traumatic shock the reduction in blood volume can be entirely accounted for by fluid loss in the region of injury. Their evidence however lacked the essential information that could have been supplied by determinations of blood volume. Direct comparison in dogs of the amount of fluid lost into the traumatized area with the reduction in blood volume has been made by Nickerson (111) and by Ashworth, Jester & Lloyd (112). The former used muscle contusion of both hind legs and measured the swelling at frequent intervals by a displacement method. The latter employed a combination of tourniquet (two hours) and blunt trauma of one leg and estimated the local accumulation of fluid after death by transection

of the body at the level of the third lumbar vertebra, bisecting the hind portion, and determining the difference in weight of the injured and uninjured side. Although the plasma dye method used by Ashworth *et al.* introduces a systematic error in their results, the estimated differences in plasma volume are probably correct and this is the important thing in the problem. Both studies prove without question that the local fluid loss is equal to or greater than the observed reduction in blood volume. Nickerson found that usually all the swelling occurs at the time of injury but that infusion of blood or fluid with rise of blood pressure at once caused further swelling.

A considerable variety of indirect evidence also refutes the concept of generalized capillary leakage. Some of this has already been mentioned, namely, that in dogs the blood volume, hematocrit, and plasma protein remain unchanged from the time injury has been inflicted until the animal succumbs. As shown by Nickerson's experiments, slight leakage into the region of injury may continue, but this is not reflected in the blood volume, presumably because fluid is absorbed from uninjured areas. Definite support for this interpretation has been obtained by blood and tissue analyses for water and electrolytes (113). Leakage is clearly limited to the region of injury. Elsewhere, fluid is absorbed by, not lost from, the blood stream (114).

The absence of any significant effect of shock on the disappearance rate of T-1824 is in accord with the facts just reviewed. Similar conclusions regarding the absence of general capillary leakage have been reached from careful studies with radio-proteins in hemorrhagic and tourniquet shock (115). Observations with radio-active dyes have also been reported in burns (116). Measurements with radioactive sodium in dogs reveal a 50 per cent decrease in the rate of transcapillary exchange (117) when shock is produced with the Duncan-Blalock press.

Hemoconcentration, once regarded as evidence of generalized leakage, has not been observed in recent studies of clinical shock except in cases of burns or abdominal injuries with peritonitis, or when hemorrhage and skeletal trauma are complicated by long exposure and dehydration. The one definite possibility of generalized leakage being the cause of shock appears with infections. Release of bacterial toxins may result in widespread damage to capillaries distant from the injured region (11, 12, 17).

*Toxic factors in shock.*—Earlier and some recent attempts (42,

43) to find a toxic factor in shock centered around the idea that harmful substances would be liberated from the traumatized region. In the main, recent work reveals three other possibilities.

Two groups of workers (11, 12, 17) have shown that in dogs clostridial infection may, under certain experimental conditions, be present and exert a definite toxic effect. Clostridia have been found in normal tissues of dogs. Furthermore, during protracted periods of hypotension and poor circulation, bacteria normally present in the gastrointestinal tract may find their way into the blood stream. In the absence of bacterial controls it is of course impossible to judge to what extent bacterial infections may have entered as a factor in many experimental studies on traumatic shock.

A second form of toxemia has come to light through studies on the circulation in small vessels and capillaries. It has been found that the blood of animals after trauma or hemorrhage contain, in the early stages, a factor which increases the reactivity of the capillaries and smaller vessels and their sensitivity to epinephrine, and in the later stages another factor which has the reverse effect, resulting in stagnation of blood in the capillary bed (46). The origin and fate of these substances termed "VEM" (vaso-excitor material) and "VDM" (vaso-depressor material) have recently been investigated by Schorr, Zweifach & Furchgott (47). The main source of VEM seems to be the kidneys. VDM is produced by the liver and the muscles in response to tissue hypoxia, the liver being the main source. It can be destroyed by normal liver tissue. The authors suggest that VDM may be the central factor causing irreversible shock. They also present the hypothesis "that the vaso-excitor and vaso-depressor principles are oppositely acting components of a homeostatic mechanism participating in the regulation of peripheral blood flow and blood pressure."

A third factor (or factors) in shock, which can also in a sense be termed toxic may be inherent in the profound changes in those normal constituents of the blood that are important in the control of various physiological mechanisms. The drop in arterial carbon dioxide, for example, has not yet been fully explored as a disturbing influence, although it is evident that it may *per se* be implicated in disturbances in circulation, respiration, function of the central nervous system, and in the intermediary metabolism.

*Nervous factor in shock.*—As noted previously severe hypotension and death from circulatory failure can be produced by prolonged electrical stimulation of the buffer nerves (31, 32). It is not

presumed however that this mechanism is involved in the usual type of traumatic shock. Observations suggesting that afferent impulses from the traumatized region contribute to the production of shock have been presented by Swingle and his co-workers (21, 118). According to their report, spinal anesthesia, local anesthesia by pressure on the extremities, or infiltration of the injured region with procaine solution reduces the mortality rate in muscle trauma experiments on dogs. However, one is forced to accept these results with reservations for there is inadequate objective proof that the severity of injury was exactly the same as in the control experiments. Production of a uniform degree of injury by muscle contusion is not an easy matter (see above). The only objective and quantitative proof of the extent to which afferent impulses from the injured region contribute to shock has been derived from evidence on the residual blood volume giving 50 per cent mortality in trauma, in simple hemorrhage (where the nervous factor is absent), and in experiments combining a sublethal hemorrhage with stimulation of the afferent nerves from the lower extremities (33). Recently Wang has also shown that traumatization of dogs, in which the afferent nerves to the hind legs had previously been severed leads to a clinical picture resembling hemorrhagic rather than traumatic shock (119) and that the residual blood volume giving 50 per cent mortality is significantly lower than in trauma experiments on normal dogs.

*Treatment.*—Investigations of the therapy of shock have naturally been greatly stimulated by the war and the literature on this important aspect is voluminous. Only a few of these studies can be considered or even mentioned here. Also a great deal of work on therapy is rather inconclusive, often lacking adequate objective criteria for evaluating either the degree of shock or the effects of therapy. The question of restoration of blood volume has been paramount. Pooled plasma, albumin, and gelatin are apparently quite satisfactory substitutes for whole blood unless the loss of red cells has been so great that the hematocrit falls to very low levels when the blood volume is restored with cell-free fluids. There are numerous and conflicting reports on therapy of hemorrhage, trauma, and burns with saline (16, 18, 120 to 130) in some of which (126 to 130) it is claimed that the sodium ion is the effective therapeutic agent. In view of the enormous quantities (15 to 20 per cent of body weight) usually necessary to produce effective results, it would seem to be a matter of maintaining blood volume by in-

creasing the interstitial fluid pressure (124). This problem is as yet unsolved.

According to a recent review of the evidence (131) cortical extracts have not proved to increase the resistance to shock. The claim that intracisternal injection of potassium phosphate is beneficial has not been confirmed experimentally (132, 133). Pressor therapy is generally considered of dubious value (133, 134, 135) and earlier claims for succinate, ascorbic acid, thiamine, or cocarboxylase have not been supported.

The relation of environmental temperature to hemorrhagic (136) and traumatic shock (14, 15) has been further investigated. In traumatic shock high environmental temperatures increase the mortality rate whereas low temperatures and local application of cold to the injured extremity is a protection against shock. In hemorrhagic shock, the mortality rate is increased by low (52° F.) as well as by high (85° F.) temperatures (136).

Much of the literature on the therapy of shock prompts one to emphasize the simple fact that the surest and probably the quickest approach to further advances in therapy is through painstaking investigation of specific disturbances in bodily functions such as those that have been disclosed by recent work. Wider application of objective criteria (chemical changes in the blood, cardiac output, blood volume, etc.) for evaluating the degree of injury or severity of shock would also accelerate progress in the testing of various therapeutic measures.

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## NERVE AND SYNAPTIC CONDUCTION

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This subject, reviewed thoroughly in past successive years, may be covered briefly this year, in view of the still cumulative effect of war conditions on research output. An attempt will be made to relate recent material to the present status of the general problems of neurophysiology.

It may be worth while to keep in mind the general goal of particular investigations of the nervous system. This is to understand the part this system plays in determining animal and particularly human behavior, including the functioning of that system in mental behavior with which the self-conscious human animal has throughout his span of history been so intensely preoccupied. On its way to attainment, this understanding can contribute to medicine in its care of the ailing, or in its protection of the healthy against ailments. The current activities of a significant proportion of the human race bear evidence of a further need however, to analyze the activities of "normal" individuals or of groups which involve other humans. The activities in question make use of biological urges which in themselves have not usually been considered pathological. These activities are likewise those of nervous tissue in action, and their devastating course is no better understood than are the courses of those minor deviations from the average which medicine is wont to call pathological. Still in every psychic or motor act there must be a physiological activity of nervous tissue; physiological and psychic behavior being the same phenomena as examined by means of different physical and philosophical instruments.

If behavior is a function of the pattern of activity of neurones built into a nervous system, only the most limited elements of that pattern are capable of being investigated by present physiological techniques. But all phenomena of nervous system activity must comprise some greater or less degree of elaboration of a process

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consisting of excitation at one or more points, conduction to other points, integration of the resultant activity in a center, and activation of effector organs. It is work on restricted fragments of these simpler patterns which is available for the present report. A current review of impulse transmission will necessarily fail to present the forest, because its assignment is so specifically to examine the trees.

*Excitation and conduction.*—There seems to be evolving a fair degree of agreement concerning the activity of nervous tissue on the following propositions: (a) All excitation may be thought of as one essential process, varying in details at different loci and under different conditions, chemical and structural. (b) Conduction in nerve fibers consists in the reinstitution of a local excitation by a previous excitation, at successive points. (c) The site of the impulse activity is the cell membrane, involving a potential across it supported by metabolism of the cytoplasm or axoplasm. (d) Under appropriate stimuli the resistance of this membrane collapses and current flows from adjacent regions, inducing an electrical sign of the discharge of the membrane's energy through the lowered resistance. This flow of current seems in fact to be the essential agency in conduction by re-excitation, as the change in resistance may be the central phenomenon of excitation in the first instance. (e) Conduction across synapses consists of the reinstitution of a local excitation across the discontinuity between cells. (f) Such transition points as the nerve-muscle junction or sense organ-nerve junction may differ from nervous synapses only in chemical and structural particulars.

Thus granting that any electrical flow through a biological structure must have a chemical source of energy, and produces a chemical effect, nervous tissue is essentially an electrochemical system. The time-intensity course of the current flow puts certain limitations on, but does not identify, the chemical processes underlying it. This fact permits a great freedom of speculation as to what particular processes are involved at different sites, and the testing of such speculations constitutes much of the current work.

The giant fiber system of *Lumbricus* has been reinvestigated (1). It presents the situation of a pair of fibers connected by commissures permitting each to excite the other. Transmission across what appear to be junctions between segments takes place, reversibly and without a synaptic delay. A larger unpaired central fiber

shows faster conduction, but lower amplitude of spike, than the lateral fibers (possibly because the latter fire together), and transmits excitation from the anterior region of the body surface to muscles of the posterior. The lateral fibers transmit from the posterior segments to the anterior muscles, and the two systems do not overlap in this respect. Rate of conduction increases with extension of the worm.

The effects of paralysis of nerve by pressure may be differentiated from those due to ischemia alone, to which latter, changes in myelination short of axonal degeneration are assigned (2). Motor fibers succumb before sensory, and when degeneration involves only the sheaths, failure of conduction does not result in muscle degeneration. The fibers below the block remain normal, and their maintenance of muscle in a normal condition without activating it is taken as a purely trophic effect of innervation. The passage of the action current over the veratrinized muscle fiber abolishes the negative after-potential as well as resting potential, although summation effects indicate that the previous after-potential is restored following an interposed spike (3). This suggests separate processes for spike and after-potential, as if some substance produced in a first excitation persisted through the depolarization by a second.

Emphasis in work on the excitatory process seems to be shifting from concern with electrical versus chemical transmission, to the question of the relation of chemical and electrical phenomena in the institution of the impulse. That excitation in general has an electrical sign, and that the chemical environment may affect both the intensity of response and the ability of the adjacent tissue to be excited in propagation, has been obvious enough. The question is, can one or another chemical phenomenon be considered the one essential of excitation, say of the change in the membrane's resistance, viewing other agents as modifiers of this process.

A résumé of the findings (4, 5) on the physical properties of irritable tissues includes the inference that a change in concentration of ions within the membrane, particularly potassium ions, may account for the change in resistance observed during flow of action current or of applied currents. The generation of current by frog nerve is considered (6) following a previous study of the relations of potassium, phosphate, and oxidation (7) to nerve potential. The source of a maintained current is assigned to glycolytic phosphorylations inducing a Donnan effect at the membrane,

rather than to potassium ion concentration. A constant EMF is maintained under various conditions which vary nerve resistance, current flow and thence the drop of voltage across the external resistance, as usually measured. The effects of calcium, magnesium, and potassium ions on rectification and on injury potential can be differentiated not merely as opposing factors, but as affecting different functions, which may appear however as opposite actions in the general overall properties of nerve (8). The suggestion (9) that a high concentration of potassium favors energy-rich phosphate compounds in carbohydrate metabolism of brain tissue implies a further involvement of potassium in the source of nerve potential, as contrasted with its possible role in permitting the discharge of the action current (10).

In contrast to the conception of potassium ion concentration involvement in potential development, acetylcholine has been advanced as not only a chemical transmitter of excitation between cells, but as the agent through which the significant potential changes are produced at cell or axon surfaces. An earlier account (11) of the action of several substances at an oil-salt solution interface at which acetylcholine was reported to give surprisingly high potentials, assigned the potential to preferential solution of organic bases in the oil, leading to imbalance of chloride ion. This is followed by further reports on acetylcholine in the presence of different oils, at different concentrations and at different temperatures (12). Lecithin and cholesterol dissolved in benzyl alcohol give considerable potentials against salt solution when small amounts of acetylcholine are added (13), while triglycerides act similarly with epinephrine, suggesting an explanation of action at cholinergic and adrenergic nerve endings. When a benzyl alcohol extract of frog and dog tissue was employed, similar potentials were induced by acetylcholine (14). It is suggested (15) that such a potential may play a role in the development of the nerve impulse, without specific statement of how it might participate in the process of excitation.

From another approach, the estimation of the amounts and activities of acetylcholine esterase in tissues, a more detailed explanation is proposed for the initiation of the nerve impulse (16, 17). The ester is released by the stimulus, and secondarily depolarizes the membrane by reducing its permeability. The esterase present then disposes of the acetylcholine, permitting recovery of the



initial potential. The concentration of esterase is estimated to be sufficiently high to permit removal of ester within the time of the action current flow; and the flow from adjacent regions is inferred to activate ester there to account for propagation. Another enzyme has been found in nervous tissue capable of anaerobic synthesis of acetylcholine in the presence of adenosinetriphosphate. The fact that large concentrations of either choline or acetylcholine applied to nerve does not induce significant potentials (18) is accounted for (16) by the assumption that these substances do not penetrate the nerve sheath, whereas the reactions involved in excitation must be intracellular.

From still a different angle, a model consisting of a metal electrode in contact with electrolyte and polarized from an external source is proposed as a means of interpreting some of the properties of irritable tissues (19). A second paper (in manuscript) deals with striking similarities in the behavior of this model and plant membranes, with respect to resistance changes and oscillatory phenomena induced by applied currents. This electrochemical system differs from the iron wire model in that true passivation is not involved in the phenomena studied, but the activity consists of a fluctuation between "activation" and a medial state. In the latter, a coating of salt, which can either cover more or less surface, or cover it more or less densely, varies in resistance complexly with changes in current flow. Changes in resistance and oscillations of current overtly similar to those of excitable tissues are analyzed in terms of chemical and physical changes in the electrode surface layer.

From one point of view this system might be considered as an analog of a biological surface in terms of electrodeposition at an oxidation-reduction interface, and this is the view presented. Alternately one might understand that both excitable tissues and such interfaces as this belong to a class of systems which contribute similar physical properties to an electric circuit, consisting of polarization capacity and a resistance variable with passage of current, acting in some respects as an inductive reactance. Together with work on polarization and rectification phenomena in nerve (6, 10), this work raises again the significant question of whether the biological membrane is to be considered as an oxidation electrode, or as a concentration interface.

Whatever the origin of its potentials, the nerve membrane

still has the properties of a leaky condenser. The charge in that condenser has been in general inaccessible to measurement except perhaps in terms of nerve threshold. For different time-strength curves a constant potential of stimulus "artifact" may be detected corresponding to the nerve threshold (20), and the constancy of this potential at threshold for varying forms of current supports the view that a specific degree of depolarization at a critical interface corresponds to excitation, whatever other component of current is ineffective.

The character of the excitation of muscle and of the neuromuscular junction presumably has general significance in the problem of excitation. In the current paper of an impressive series (21) a comparison of the properties of the muscle endplate with those of the rest of the fiber is presented. In this, as well as in a previous paper (22) on the effects of calcium, the endplate is presented as selectively depolarizable by lack of calcium, by acetylcholine, etc., as compared to the fiber elsewhere, but otherwise has the same excitability to an applied brief electrical stimulus. Under drug action, spontaneous activity originates at the margin between endplate and the rest of the fiber, due to depolarization of the endplate up to that margin, and repetitive firing results from application of agents which increase the effective duration of the endplate depolarization. Similarities to the action at sympathetic synapses reported elsewhere (23) are noted. This reviewer generalizes, from some rather cautious statements, that electrical depolarization induced by drugs or by the electrical impulse is the immediate stimulus to the muscle fiber; that the endplate region differs from the rest of the fiber in being easily and characteristically depolarizable, to give the endplate potential; that the endplate region may also conduct a normal spike process; and that the depolarization induced by the nerve impulse as the endplate potential is of the same nature as that induced by any depolarizing agent there, except for its time-intensity course which is normally a function of the energy delivered by the nerve and of the state of the endplate. The significance of the endplate differentiation from the rest of the fiber might then be that it makes possible a boundary between depolarized and nondepolarized tissue, at which a concentration of endplate depolarization current can set off a full spike process. If this is the state of affairs, it would follow that the secretion of a neurohumor at a junction and the flow of action

current across it should induce the same effect in the next element, and much of the energy expended on debate as to which of these is "the" transmitter can now be redirected. (See below, *Synapse*.)

*Chemical factors in excitation.*—Aside from the chemistry of nerve metabolism as such, work on the chemistry of certain substances supposed to be involved in excitation may be considered here. The synthesis of acetylcholine by fresh brain on grinding, and by dried and powdered brain in the presence of physostigmine is demonstrated (24, 25). Ether increases the synthesis; glucose inhibits at normal blood concentration. Cholinesterase in peripheral nerve is not decreased by freezing, drying, and rehydrating and pseudo-esterase found there is not present in brain tissue (26). The distribution of both true and pseudo-esterase in the sympathetic system indicates greater concentrations in synaptic regions, and pseudo-esterase is thought to be located in cell bodies, true esterase in preganglionic fibers and endings (27). Esterase decreases after preganglionic section at the same rate in both fibers and ganglia. The distribution of acetylcholine in various parts of the nervous system shows a concentration which is low in the cerebellum and increases progressively through cortex, brainstem, cord, and peripheral nerve in that order, with a maximum increase of thirty fold (28). With exception of the cortex, the concentration is estimated to be proportional to resistance to anoxia, and to oxygen and glucose utilization and glycogen storage. In brain slices, a high potassium concentration increases synthesis of acetylcholine (9); it is suggested that potassium is involved in carbohydrate metabolism through its effect on phosphorylization by furnishing energy for the synthesis.

The action of acetylcholine in the rectus muscles of frogs is increased by carbon dioxide, which is referred to the anti-cholinesterase activity of this substance in protecting acetylcholine (29). The intensification of many "cholinergic" reflexes by acid, as by physostigmine, is assigned similarly to the effects of acid on esterase (30). Particularly in respiratory reflexes, the effects of acid metabolites on acetylcholine as a generator of depolarizing current at the neurone surface is considered, and the experimental findings are employed to elaborate more fully the electrotonic concept of synaptic activation (31). Alterations of blood pH induce striking changes in the central nervous system, particularly in reflexes, which are decreased or abolished by increased acidity (32).

The depletion of Nissl substance in chromatolysis after nerve section (33) is related to acid phosphatase activity involved in the synthesis of material for growth of new fiber, this concept amplifying a previous opinion (34) that Nissl changes involve dispersion of ribonucleotides as a step in mobilization for growth. The stages of the Nissl histological picture during regeneration can be correlated with the presumptive need for materials at the growing region, which must then migrate from cell body through the length of the axon.

With the studies of the chemistry of chromatolysis may be considered the physiological depression of cell function that accompanies nerve section. Retrograde degeneration abolishes the two-neurone arc reflex leaving the multineurone arc intact (35), and on antidromic stimulation of the stump of a previously cut motor nerve (36) the cord potential assigned to the cell body is depressed as compared to the nearly normal spike of the nerve. This suggests the greater vulnerability of the cell body (as an element of the synaptic complex) to depression than that exhibited by nerve fibers raising again the question as to what portion of this complex may be identified with synaptic properties, and what the essential properties of a synapse are.

*Synaptic function.*—Since it is permissible to view the synapse as a special case of the excitable structure of nerve, the subject can be dealt with from two viewpoints; first, in what respects does the synapse as such differ from the nerve fiber, and second, what conditions in the body might modify the function of this labile and critical region.

Anatomically the minimal essential of a synapse is a discontinuity between two elements, and its properties are critical because of its ability to act as a switch in an otherwise uniformly conducting circuit. To make such a switch significant in a nervous system, however, something must throw the switch, that is, the junction must for some reason be more sensitive to available forces than is the nerve fiber. In the simplest junction-like structure available, the septa across the giant fiber of *Lumbricus* (1), it is not certain that such a structural discontinuity exists, and at least no sign of conductive discontinuity is apparent, although histologically the septum stains like nerve sheath. It suggests the possibility however that a mere structural partition is not a critical factor, provided that the two segments approximate each other efficiently, are

of equal size and energy output, and neither is significantly, or both are equally, polarized. A definition of significant requirements for a synapse is implied as the opposite of these.

A "synapse" might then result if any two separate elements were applied one to the other in such a manner than the impulse of one excites the other to response. The long-known rheoscopic frog preparation was the first of these, and in fact it exhibits polarization of an obvious nature; the muscle impulse stimulates the nerve, but the nerve impulse does not stimulate the muscle. The reasons are both geometrical and functional. Arvanitaki, in a series of papers, has described a fiber-to-fiber synapse, which was able to conduct if in effect the excitability of the receiving fiber was increased more than the power of the sending fiber was decreased. Such a junction is not necessarily polarized, but may conduct reciprocally. While some further differentiation between sending and receiving element is necessary to produce a discriminating or selective synapse, this reciprocal system is a model for some of the structures reported on currently. An obvious challenge is offered to find methods of rendering such a junction irreciprocal.

In junctions of this type, such as between parallel fibers at an injured or cut region (37) or at the branch of a nerve where the subthreshold exciting effect of impulses in one fiber bundle may be observed in an adjacent bundle (38), the flow of electrical current itself is the obvious agent acting across the junction. Any polarity at such a site is a result of the spatial and conductive relation of the fibers, and such a system offers an excellent opportunity to observe the effects of a geometrical factor that is obviously active in any naturally occurring synapse. Below threshold at such a branched region either an increase or a decrease of excitability can occur in one bundle due to flow of action current from the other, depending entirely on the physical circuit obtaining and corresponding superficially at least to facilitation and inhibition at synapses. At the cut end of a nerve (39, 40) lowering the temperature increases the spike height and duration, decreases accommodation, and sets up polarizing currents by reason of temperature gradients. The sum of these effects serves to increase the energy of the sending fibers at the same time as it increases the sensitivity of the receiving fibers, thus resulting in facilitation of transmission. While it is improbable that temperature differences normally affect true synapses significantly, the experiments suggest that

agents other than temperature may operate correspondingly in the central nervous system, and they also may account for effects observed in certain experimental situations as a result of cooling.

Granted the dependence of transmission on the geometry of current flow, from the impulse of one element to an excitable point on the next, and ignoring for the sake of simplicity the problem of summation of more than one impulse to activate a transsynaptic element, any further differentiation of one element as to energy output or the other as to sensitivity to stimulation will give a junction a more specific character. At one extreme lies the juxtaposed nerve fiber pair, with flow of current as the obvious agent of transmission, whatever the chemical effect in the excited fiber. At the other extreme may lie the junction of the sympathetic fiber and smooth muscle, where some epinephrine-like chemical agent secreted at nerve endings is perhaps the predominant form of energy activating the muscle. At many other junctions "secretion" or chemical activation appears to take place, at least as an assistant to synaptic passage of the impulse, and this increasingly appears to involve a special utilization of substances which are otherwise utilized in nerve metabolism generally or in the chemical cycle of impulse generation of the fiber. It would not be surprising if different synaptic junctions showed a different distribution of emphasis, or different dependence, on current flow and on the chemical products of an electrochemical process. This would seem to be a reasonable manner in which the differences which exist at different junctions could be provided for. It might even correspond to the fact that, in studies by electrical means, electrical effects may be predominantly observed, and in studies pursued by chemical means, chemical effects.

From this point of view, no sharp line need be drawn at present between the effects, on sensitivity of the transsynaptic element to the impulse of the presynaptic, of autogenous products elaborated in connection with the impulse, and of substances introduced. For instance small quantities of epinephrine perfused through the cervical sympathetic ganglion increase, larger amounts decrease, response of the nictitating membrane to nerve stimulation (41), similarly to acetylcholine which is apparently produced there. Parathyroid removal, like citrate (low calcium), increases the excitability of the muscle fiber and also increases the activity of the central nervous system (42) The muscle may thus give a repetitive

response to one nerve impulse, as well as receive more than normal impulses, in a manner fairly well elucidated by previous studies of the nerve-muscle junction and of the cervical sympathetic synapse (23). The list of other substances or agencies which must exert their effects by modifying the activity at synapses is extending rapidly, although in few cases can the action be so specifically designated as in the above instances.

The influence of gonads and adrenals on brain chemistry is of interest in connection with the obvious changes in pattern of nervous behavior in phase with the sexual cycle (43). Depletion of electrolyte and glucose alters the pattern of spontaneous activity recorded as the electroencephalogram of frogs (44) producing slower waves; restoration to normal by sodium chloride is possible. The effect is assigned to depression of oxidative metabolism of glucose. The excitability of the central nervous system to direct or reflex stimulation varies with the pH as modified by injection of buffers into the blood (45), and the effect can be assigned to the synapses traversed, not to the site of stimulation. This may be considered in relation to a previous report (46) that if the pH is held constant anoxia produces a minimum of its usually observed effects, and in relation to the effects of acid metabolites (31). Anoxia stimulates spinal cardiovascular centers directly after cord section and deafferentation, but carbon dioxide in the presence of sufficient oxygen does not stimulate (47). The relation between the effects of changes in blood sugar level and of hyperventilation on the electroencephalogram (48) and changes in brain potentials induced by high oxygen tension (49) presumably falls in the category of synaptic excitability changes due to changes in metabolism, and references in previous literature significant in this respect are numerous. The Symposium on Cerebral Circulation (50) contains, incidentally, many references to the effects of circulatory supply on what must be synaptic function. Unfortunately, detailed examinations of specific synapses in the central nervous system are more difficult than at the myoneural junction and in outlying ganglia, and explanation of the detailed action of the agents employed to modify transmission over central synapses is therefore highly inferential. There is sufficient reason to conclude provisionally however that the differences between central and peripheral junctions, or labile and less labile ones, may be in a sense quantitative rather than qualitative.



Still further removed from specific analysis are findings on the effects of head injuries in dogs (51), and in human accident cases (52, 53), where paralysis is induced apparently independently of the stimulating effect. Conditioned responses are interfered with more than deeper lying functions, and such tests are considered more discriminating than are changes in the electrical brain record. Three papers on the spread of a depressing effect of stimulation across the cortex (54, 55, 56) trace such propagation through the upper layers of the cortex and via the corpus callosum rather than through thalamic connections. A profound dilatation of pial vessels accompanying the depression may be the immediate event, rather than neurone-to-neurone inhibition. In that case it would seem to be the excitation which spreads, followed by dilatation and depression.

In summary, current work involving synaptic function connotes two types of effects: one transitory and associated with the nerve impulse and its immediate after-potentials, the other persisting over a considerable time. The latter may result indirectly at least from nerve impulses, as is indicated by such findings as involve changes in circulation and pH associated with activity, etc. The former requires virtual synchrony of two or more impulses for their mutual interaction and integration of response. Experiments in which two or a few impulses are summated at a synapse, and which indicate a prompt disappearance of effect with subsidence of the impulse, may not involve sufficiently complex activity to tell the whole story of synaptic excitation. The problem of analysis of the response of complexes of neurones as the correlate of behavior is progressing, but is still in the stage of conjecture.

*Inhibition and facilitation.*—Continuing interest in the phenomenon of inhibition involves the exploration of its pathways rather than the nature of its action. It is becoming increasingly evident that inhibitory pathways are distinct functional components of the nervous system, i.e., mechanisms devoted exclusively to suppression or modulation of activity. The "state" of the nervous system, that is the level of excitability of its synapses, is a result not only of the factors noted above, circulation, metabolism, secretions, etc., but of the balance between facilitory and inhibitory impulses arriving at synapses. If any cells of the nervous system are truly spontaneously active, that is if their excitability rises above the threshold of discharge due to their own metabolism, modulation

of that activity can be presumed to include both increase and decrease by nervous impulses arriving at their surfaces. Inhibition may be interpreted not merely as absence or blocking of excitatory impulses, but rather as the reciprocal of excitation.

In the cord, stimulation of a peripheral nerve modifies the response to a later test shock applied to a locus in the grey matter, facilitating or depressing in a rhythmic cycle (57, 58). Whether this can be assigned to recirculation of impulses in closed circuits or whether it represents cyclic activity at one locus is not clear. Post-inhibitory rebound becomes in this scheme the facilitatory phase of the cycle. Transection of the brainstem at various levels produces selective and enduring decrease of reflex activity, presumably by removal of tonic facilitory impulses, centers for which are distributed along the brainstem (59). From the parietal lobe, fibers traced to the cord are assigned the ability of facilitating activity of spinothalamic neurons (60). The suppressor areas of the cortex have been stimulated in man (61), and a worthy attempt is made to define the connotations of the terms "suppression," "inhibition," and "extinction" as applied to the complicated depressing effects of stimulation of the cortex. The inhibitory system of the cerebrum is given a certain pattern of organization by the finding on the gyrus cinguli of an area receiving connections from all suppressor areas but projecting to none of them (62). The functioning of this region in relation to peripheral activity has been studied by means of electrical stimulation (63). Inhibition of somatic movements and of reflexes, abolition of after-discharge, and reduction of the response to stimulation of the precentral cortex are observed, together with activation of autonomic and respiratory inhibitory centers.

In preliminary reports with few details, the peripheral connections and action of the cortical inhibitory system are outlined. An earlier study (64) of the results of section of the peduncles in the monkey, wherein section induces a condition with some of the aspects of both spasticity and paresis, indicated that not all inhibitory paths from the cortex pass through the peduncles, some leaving the main descending bundle above this level, and some just before reaching the pyramids in the medulla. An inhibitory center is now found in the bulbar reticular formation of cats and monkeys (65) which is activated by stimulation of area 4S of the cortex (66) and which upon direct stimulation produces widespread inhibition

of spinal and cranial reflexes. It also depresses decerebrate rigidity and spinal activity originating in the motor cortex, and appears to be a discrete continuation of an extrapyramidal depressor system devoted to modulation of the activity of the final common path neurones or of their internuncials. Effects of concussion on reflex activity may involve this bulbar center (67).

In continuing studies of auditory fibers (68) showing inhibition of activity due to one tone through stimulation by another, the auditory tract is found to contain elements which respond to sound, and others only to cessation of sound, in patterns quite similar to those known to be present in the optic nerve (69). The effects are attributed to inhibition in the periphery, as previously accounted for in the retina (70).

*Organization and activity of the central nervous system.*—Aside from items concerning electroencephalography as such, not dealt with here, a number of papers deal with brain potentials under experimental conditions. The effects of anaesthesia on brain potentials is compared to sleep in cats (71). Cutting or stimulation of the facial nerve, which supplies parasympathetic fibers to pial vessels, modifies the potentials of the brain under hyperventilation (72, 73), the effects being mediated through the blood. Stimulation of the posterior hypothalamus alters the threshold for electrical stimulation of the cortex, presumably assignable to sympathetic activity (74). The olfactory system of cats has been outlined, and its structure analyzed by electrical techniques (75). Pathways from the ear are followed by electrical recording (76) with findings that the contralateral record is slightly greater than the homolateral at the inferior colliculus level, that many fibers by-pass the inferior colliculus, and of those which enter it, many discharge by way of the superior colliculus pathways. The projection of the retina on the anterior corpus quadrigeminum of the cat shows a definite pattern comparable to the projection of the cortex, the temporal retina projecting homolaterally (77).

Plots of the potential throughout a single level of the spinal cord following single shocks to a dorsal root give contour maps at different instants after stimulation, and offer a graphic method of tracing the pathway of activity through the cord, at least in two dimensions (78). Slow potentials are interpreted as after-potentials, rather than as responses of internuncials, although such interpretations on the basis of polarity seem somewhat equivocal. The spike

of the afferent of the two-neurone arc can be traced to the region of the ventral horn cells, followed after a synaptic delay by a ventral horn cell potential, recorded as a positive deflection. Two components of the dorsal root potentials elicited by stimulation of a separate dorsal root differ in that the earlier is not increased by strychnine but is blocked by section of the dorsal column, while the second is increased by strychnine and takes a devious course through synaptic junctions (79). The first is thought to be mediated by direct contact between parallel fibers. The response of vasodilatation to depressor nerve stimulation has been reinvestigated (80) and absence of depressor dilatation after root section leads to the conclusion that the root constitutes the efferent pathway for the reflex. The role of proprioceptors in influencing the frequency of reflex clonic shivering is demonstrated by loading the muscles with weights so balanced that they have their own natural period (81). The shivering then follows this frequency. From buried electrodes single and repetitive shocks in cortical stimulation are employed to follow changes in excitability resulting from previous cortical activation under convulsants and anaesthesia (82, 83).

*Mathematics of nervous networks.*—Papers appearing over several years and dealing mathematically with certain phases of nervous system activity have received slight notice from reviewers, and probably from physiologists in general. The present writer, being unable to understand even the notation of this treatment, presumes to infer that his own disability is general enough among physiologists to account for the neglect, without prejudice to the merits of the work itself. After some consultation with persons more competent than himself, the following evaluation of the significance of these ventures for physiology is offered as a tentative and quite nonmathematical estimate.

Several steps are necessary if mathematics is to contribute to nerve physiology more than the computation of its data. The first essential is to restate the findings of physiology in terms intelligible to mathematicians, and this translation into a mathematical notation comprises a considerable part of the work so far, though it cannot yet be said that the inverse of this relation obtains. A second is to formulate in mathematical symbolism the problems to be dealt with, and to check the solutions against experimental fact. First attempts at this critical function have been made, often with what seem to be such arbitrary simplification as to leave the result

more of a trial survey than a useful tool. Further progress in this direction may be expected to furnish both a check on the logical validity of inferences from data, so confusing in their physiological details, and to suggest further problems or approaches for experimental work. Finally it may be hoped that having restated and organized in symbols mathematically adequate a sufficient amount of biological information, problems that are almost impossible to deal with experimentally may be handled in a theoretical manner. The complexities presently obvious in the nervous system as a network of unit neurones are probably too involved to be dealt with by present or immediately prospective physiological techniques. A logical simplification in terms of mathematical symbolism may offer a means of both analyzing and predicting possible patterns of action, which can then be compared with overall behavior of larger complexes of neurones than can be dealt with in detail.

Above the elementary level of the problem of the nature of the nerve impulse, the problem of pattern, structural and functional, is the central one of neurophysiology. This has been attacked in recent papers (84, 85) and the convenient datum that the nerve impulse is a unit of energy discharge, i.e., all-or-none, suggests an approach to the flow of impulses through nerve networks without involving the question of how the impulse originates in a fiber. To the extent that actions of synapses are not unitary, but qualitatively or quantitatively variable, either by reason of the character of the essential activity there or of the multiplicity of factors that modify the excitability, the adequacy of the assumptions so far incorporated into theory might be questioned. A proposal which may obviate some of these difficulties (86) is to treat groups of synapses as units, permitting simplifications of a general theoretical treatment of complex networks. Possible shortcomings of such a viewpoint need not embarrass mathematicians however until physiologists have offered them a closer acquaintance with the synapse than is available at present. The problem is to state mathematically the fundamental properties of nerve networks as they are now known, and to furnish a theory of networks that will cover any temporal-spatial pattern of activity.

From a different approach (87) the notation and technique of propositional logic are applied to the organization of certain of the properties of nervous tissue into a general functional system. It is proposed that an impulse traversing an element of pathway is com-

parable to a simple proposition, and that impulses traversing networks can then be dealt with by methods of logic applicable to the relations between propositions. This paper is not for the lay reader. A sequel, if it be that (88), offers so intriguing a treatment of reflex and central organization that, like the denouement of a mystery story, its solution should not be divulged in a review.

Finally, a monograph (89) summarizes the mathematical approach to many problems on the psychological as well as the physiological level. As the authors suggest, the work so far is tentative and preliminary, and perhaps furnishes little of practical utility to the physiologist in the laboratory. Its further prosecution may be expected to furnish a critique of physiological theory, and may also be so fortunate as to extend that theory beyond the limits of experiment. Before that happy consummation it will be well either for physiologists to familiarize themselves with mathematical technology, or for mathematicians to elaborate at least their conclusions in a less formidable language.

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## THE VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM\*

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### INTRODUCTION

The dichotomous classification of the autonomic nervous system into sympathetics and parasympathetics, which carry on a perpetual tug of war, is an oversimplification zealously nurtured in biological teaching. An astute British physician (1), surprised by the clinical results of lumbar sympathectomy, commented "possibly the paradox lies in our conception of an essential opposition in the action of the two systems, an idea encouraged by much biological teaching." But the most articulate critic of this artificial concept is Langworthy (2) whose "General Principles of Autonomic Innervation" makes a good introduction to this review. He challenges the widely accepted dictum that the sympathetic and parasympathetic systems are functionally antagonistic. The opposition which has been attributed to the two types of innervation of the bladder and of the eye becomes unreal in the light of experimental findings. Langworthy has formulated a more likely hypothesis of the relations of the sympathetics and parasympathetics to each other and to the somatic nervous system.

The somatic motor fibers are of the highest differentiation, are most dependent on control through the central nervous system, and are under the greatest voluntary control. The sympathetic fibers show the least differentiation, are least dependent on control through the central nervous system, and are least responsive to voluntary control. The parasympathetic fibers hold an intermediate position. When both sympathetic and parasympathetic fibers innervate a single organ, such as the iris, the urinary bladder or the gastrointestinal tract, it is probable that the sympathetic system exerts its influence solely through the medium of the circulation, and the parasympathetic fibers through actual innervation of the smooth muscle.

This hypothesis in no way disturbs the older concepts of anatomical division and chemotransmission in the autonomic nervous system. It does, however, attack the theory of dual innervation of an effector organ, and thereby the traditional idea of antagonism.

\* This review covers the period from April 1943 to August 1945.

## EFFECTORS

*Pupil.*—For some years the reflex regulation of pupillary size has been attributed more and more to fluctuations in the discharges through the ciliary ganglion, and the role of the sympathetic innervation has been progressively minimized. Anatomical studies of the iris by Langworthy (2) have provided a sound structural basis for the revision of the older concept. Dilation of the pupil in response to painful stimulation of afferent nerves is now generally recognized as inhibition of the oculomotor nerves; the central pathways traversed by these afferent impulses are separate throughout their course from the lateral spinothalamic tract, so that the sensation of pain and dilation of the pupil are mediated through distinct mechanisms (3). Inhibition of the third nerve nucleus is also an important component of pupillary dilation in anoxia (4).

Constriction of the pupil in response to light is normally a smoothly integrated response, in which the pupil rapidly becomes smaller and remains so as long as the light is constant. Early in pathological conditions which affect the reflex arc, this precise modulation is impaired, so that if a small beam of light enters the periphery of the pupil to reach the retina, the pupil constricts; when the light beam is interrupted by the iris, the pupil again dilates, and the procedure is repeated again and again (5). The pupillary light reflex contains, somewhere in the arc, a cholinergic transmitter, for the injection of cholinesterase preparations diminishes or totally abolishes the response (6). It may be that the last link in the arc, the terminations of the nerve on the sphincter pupillae, is the one paralyzed by the enzyme. Armstrong has shown a high concentration of the esterase in this site in the turtle's eye (7), while in the amphibian eye the concentration is low (8). He suggests that there may be two types of cholinergic nerve endings: those rich in cholinesterase and those poor in the enzyme; and that these be called "esterasopenic" and "esterasopenic" respectively (9).

*Gut.*—The generalization that parasympathetic nerve fibers go to the muscle of an organ, while the sympathetics go to the blood vessels, can apparently be extended to the stomach. Langworthy & Ortega (10) have studied, with the methylene blue technique, the innervation of the stomach of the cat, and have found four types of nerves. Of these three are in the smooth muscle layer. The

first group, presumably postganglionic parasympathetic, runs parallel to and ends upon the smooth muscle cells; a second group, constituting a fine network of small fibers arborizing about the smooth muscle of arterioles and capillaries, is considered sympathetic. The third group, made up of myelinated fibers, has endings comparable to the proprioceptive endings in skeletal muscle, and is thought to be sensory. A fourth type of ending is found in the subserosa. An exclusively parasympathetic innervation of the gastric musculature is suggested by Jones (11), who showed that bulbar or sacral lesions in chicks prevented the development of an enteric plexus. The sensory innervation of the dog's stomach seems to be sympathetic, rather than vagal, passing through the splanchnics to enter the cord over the dorsal roots of T<sub>4</sub> to L<sub>3</sub> (12).

Stimulation of the vagal nerve going to an isolated strip of the dog's stomach caused only inhibition (13). In the intact dog, emotions and noxious stimuli caused an inhibition of the entire sphincter region (antrum, sphincter, and bulb), yet at the same time retarded the gastric evacuation by decreasing gastric peristalsis (14). While the nervous pathways through which this inhibition is effected are not identified, it is clear that paralysis, not pylorospasm, underlies the delayed emptying of the stomach. Wolf (15) has made observations on gastric motility in man, in one case directly through a fistula, and has observed that the stimuli which caused nausea did so only through gastric relaxation and hypomotility. If the gastric activity was sustained through the use of atropine or prostigmine, the stimuli caused no nausea.

In two patients with excessive secretion of gastric juice at night and with peptic ulcer, supradiaphragmatic section of the vagus nerves diminished the quantity and acidity of the gastric secretion and relieved the patients of epigastric distress (16). Further studies on patients with peptic ulcer has revealed two distinct mechanisms for increasing gastric secretion: the injection of insulin or histamine causes an increase in the quantity and free acidity of gastric juice, but the response to the former is abolished by vagotomy, while that to the latter is unaffected (17). Vagotomy also reduces the hunger contractions of the empty stomach (18).

The lower end of the esophagus contracts tonically after the vagus nerves are cut in the neck; this cardiospasm is presumably due to the unopposed action of the sympathetic nerves, since atropine is ineffective, while ergotamine causes a relaxation (19). Vagal

stimulation causes a contraction of the longitudinal fibers of the esophagus of such magnitude that this mechanism is considered important in hiatus hernia (20).

The possibility of intestinal reflexes being mediated through prevertebral ganglia is still debated. Freund & Sheehan (21) could find no evidence of visceral afferent neurons synapsing with post-ganglionic neurons in the celiac ganglia, but Kuntz & Saccomanno (22) have presented both anatomical and physiological evidence that reflexes can be mediated through decentralized ganglia. The latter authors (22) suggest that the sensory neurons lie in the intestinal wall and send axons to the prevertebral ganglia, where synapses permit the stimulation of efferent neurons and thus constitute a reflex arc. The reviewer does not feel obliged to reconcile these contradictory interpretations, but one factor in the experimental techniques is suggested as a possible source of the different findings, i.e., the pressures within the lumen of the gut. Peterson & Youmans (23) have shown that the intestinointestinal inhibitory reflex may be elicited with progressively lower pressures as the length of gut distended is increased. With a 5 cm. balloon, pressures of 35 to 100 mm. mercury were required. Kuntz & Saccomanno used high pressures, admittedly beyond the physiological range, while Freund & Sheehan report only that air injected into a finger cot was used as a stimulus.

The sites of action of drugs which cause a contraction of the circular muscle of the gut have been identified by Vogt (24), who used the influence of atropine and nicotine as an aid in distinguishing nerve from muscle stimulation. Potassium chloride, which causes either rhythmic or tonic contractions, acts without modification in the presence of atropine or nicotine, so that it appears to act directly on the muscle. Sodium lactate and sodium chloride cause contractions which are abolished by large doses of atropine; they act upon the myenteric plexus.

In the absence of extrinsic nerves, prostigmine and physostigmine exercise their usual excitatory action on the intestine, and furthermore atropine reduces or abolishes this excitation (25). It is difficult to reconcile this observation with the thesis that the anticholinesterase drugs excite only through the preservation of liberated acetylcholine. The authors present three possible interpretations: (a) physostigmine and prostigmine are excitants to smooth muscle of the gut, (b) they permit the accumulation of lo-

cally produced acetylcholine, or (c) they may allow an elevation of the acetylcholine concentration in the blood coming to the gut. Prostigmine accelerates the progress of a meal along the intestine; atropine retards it (26).

The motility of the large and small intestine of the dog has been measured in different degrees and types of anoxia (27, 28, 29). The cells of the myenteric plexus are among the most resistant of neurons to anoxia, and have the highest concentration of acetylcholine of any mammalian nervous tissue (30). It is suggested that the two properties are causally related.

The muscularis mucosae of the large and small intestine of the dog is innervated by both cholinergic and adrenergic motor nerves (31).

Millott (32) has shown an extensive similarity between the innervation of the gut in annelids and in vertebrates. Nerves which augment intestinal activity leave the central nervous system together with the inhibitors, but follow a different course to the body wall and along the septa to the intestine. These nerves show the same pharmacological properties which have been described in vertebrate nerves, i.e., they are adrenergic and cholinergic (33). The similarity in function and organization includes secretory tissue in the anterior intestine; the secretory cells produce protease in response to stimulation of nerves which leave the central nervous system in the same region and pass to the gut along the same course taken by the augmentor fibers (34). The full appreciation of these physiological studies can only come with a far more intimate knowledge of the anatomical relations of each type of fiber to glands, intestinal muscle, and blood vessels. It may be that secretion of enzymes is secondary to vasomotor change, and that inhibition of the gut results from chemicals released by the nerve terminations on the vascular bed to the muscle. Fortunately Millott is extending his studies to include this phase of the problem.

The morphology of the anterior autonomic nervous system in the earthworm has also been described and illustrated by Chen (35).

It is highly probable in the dog that the action of the vagus in producing an enzyme-rich secretion is due to its vasodilator effect; sodium nitrite, a potent vasodilator, produces the same response. On the other hand, epinine and secretin increase the flow of pancreatic secretions, but the material has a low enzyme content (36).



Prostigmine and acetylcholine stimulate the acinar cells of the pancreas, and after pretreatment of the animal with thyroxine, which sensitizes the pancreas to acetylcholine, vacuoles appear in the acinar cells (37). The vagal influence on pancreatic secretion is best shown in stimulation experiments, for when the nerves are cut there is only a temporary suppression of the secretory response to substances placed in the intestine, and the response is soon restored to normal (38). Crider & Thomas suggest that peripheral reflex mechanisms which control pancreatic secretion are modulated by impulses from the central nervous system via the vagus. Until such peripheral reflex centers are demonstrated, and they are still debated pro (22) and con (21), even for intestinal motility, they can hardly qualify as the physiological basis of experimental interpretations. The reflex mechanism through which peptone, soap, or hydrochloric acid in the intestine increases secretion by the pancreas is not clear; the response is inconstantly modified by atropine (39). Ergotamine appears to diminish both the external and internal pancreatic secretions (40).

Reid (41) has given a preliminary description of what may be an olfactory-pancreatic reflex: when a dog was allowed to sniff meat, its blood sugar fell.

The innervation of the intestine and its associated glands has never been as thoroughly analysed as the nerve supply to other systems for obvious reasons. The complex admixture of preganglionic and sensory fibers which enters the abdominal cavity soon becomes further complicated by the addition of postganglionic fibers. The location of the postganglionics makes it difficult, by surgical means, to isolate any one component of the autonomic innervation. Boyden and his students have attempted an analysis of the nerve supply to the choledochoduodenal junction to provide an understanding of their results in denervation experiments. They found that section of the vagal nerves retarded the flow of bile through the ampulla, while section of the splanchnics produced only a minor acceleration (42). Their findings suggest that the sympathetic components are sensory or vasomotor, while the vagal fibers are concerned with the innervation of the muscles of the common duct and duodenum (43). This latter is accomplished indirectly, for the vagal fibers end on an intrinsic nerve net made up of an intramural plexus in the duct and of myenteric plexus in the duodenum. Since this intrinsic plexus persists after section of both vagi and of all

connections to the celiac ganglia, it is presumed that it is the apparatus which effects emptying of the gall bladder when all extrinsic nerves are cut (44). This reasoning, like that of Crider & Thomas (38), presupposes the existence of peripheral reflex centers. Sympathetic fibers in the gastroduodenal nerve outnumber the vagal fibers, although they seem less important functionally (45). It was observed that some myelinated fibers were apparently sensory, an observation in keeping with Foley's (46) that the splanchnics are largely sensory.

The ganglionated nerve net, already described in the common duct and duodenum, extends into the wall of the gall bladder in the cat (47). The liver seems to have a pure sympathetic nerve supply; section of the vagus causes no loss of fibers in the porta, while excision of the celiac plexus removes all the nerves passing to the liver (48). The superficial hepatic branches of the vagi have been dissected in the dog, cat, and guinea pig (49).

The motility of the colon is influenced by electrical stimulation of the forebrain in the cat, but there seems to be no sharp localization of the type of response, which varied from inhibition to immediate contraction (50).

*Heart.*—A recent development in theories of the spread of excitation in the heart has been the substitution of autonomic nervous conduction for myogenic conduction. A morphological study, both gross and microscopic, of the human heart has failed to support the latter (51). In the first place, the atrioventricular bundle has no continuity with atrial muscle, but originates distal to the dense connective tissue separating the atria from the ventricles. Furthermore, Glomset & Birge (51) found no bifurcation of the bundle and therefore no left branch. They have centered their attention on the intrinsic nervous system consisting of postganglionic neurons, scattered or in small ganglia, which lie beneath the pericardium, and of nerve fibers which accompany the coronary arteries or pass as trunks to the ventricles. They make no attempt to identify these nerve fibers. Nonidez (52, 53), studying the cat, dog, and monkey heart, and Woollard (54), studying the cat, dog, rabbit, and guinea pig heart, believe most of the fibers to the ventricle are sympathetic, and that few if any parasympathetics, either pre- or postganglionic, cross the coronary sulcus. Kaylor (55) has found, however, that in the heart of the newborn guinea pig, parasympathetics (identified by the staining reaction with Cajal's silver

nitrate method) go to the ventricle and are distributed along the branches of the atrioventricular bundle. Kaylor finds that the atrial muscles and the sinoatrial node receive very few vagal fibers, and responses to vagal stimulation correlate nicely with the anatomical findings, since the ventricles respond sooner and to a greater extent than the atria. While the foregoing work of Kaylor seems to support the theory of Glomset & Birge, Robb & Kaylor (56) have recently reported that in the guinea pig heart the atrioventricular node lies in the posterior part of the interatrial septum and that the main bundle with the right and left septal branches can be followed in serial sections to their peripheral connections with the ventricular muscle. A similar study of differentially stained serial sections of human tissue must be made before the anatomical basis of myogenic conduction in the human heart is rejected. Nonidez (53) has already described the conducting system in the dog and monkey. He found the atrioventricular node to be a richly innervated zone of transition from atrial muscle at the periphery, through a reticulated tissue, to the central compact node; the last is continuous with the main atrioventricular bundle. The nerve fibers to this system arise from neurons in the coronary sulcus or on the atrial muscles above it.

The differential innervation of the dog's heart by the right and left vagi was studied in unanesthetized dogs through the use of reflexes originating in the vasopressor action of pitressin and neosynephrin (57). The cardiac response was determined from electrocardiograms. When the left vagus was intact, the response to the pressor compounds was sinus bradycardia commonly accompanied by atrioventricular block; when the right vagus was intact, the heart also slowed and the sinoatrial node was frequently so depressed that an atrioventricular nodal rhythm was recorded, but no atrioventricular block occurred. In puppies, in contrast to adult dogs, epinephrine causes a slowing of the heart which is not mediated through the vagi, but apparently through inhibition of the sympathetics (58). The heart can be slowed by a conditioned reflex (59).

The action of the vagus or of acetylcholine on the heart can be greatly modified by changes in temperature, but the nature of the change varies with the species. The isolated molluscan heart, which is relatively insensitive to acetylcholine at 25° to 30°C., becomes one hundred times more responsive at 5° to 10°C. (60). But the

heart of the frog shows an increased responsiveness to vagal stimulation on the application of warmth (61). This sensitivity of cholinergic systems to temperature has been observed in other tissues, and Ambache *et al.* (62) attribute the inhibitory effect of cooling on the crop and gizzard of the earthworm to cessation of acetylcholine synthesis by the nerves, since, in the cold, the muscle is still responsive to the drug. They have taken advantage of this to study the mode of stimulation of muscle by potassium, which they found to be ineffective in the cold, but active in warm preparations and potentiated by physostigmine. They conclude, of course, that potassium acts by release of acetylcholine. Furthermore, according to Hoff *et al.* (63), the potassium concentration in the plasma is directly related to the effectiveness of vagal activity, whether elicited reflexly or by direct stimulation.

Further evidence that the vagus acts through the liberation of acetylcholine has been obtained by determining the minimal frequency of vagal stimulation which will stop the heart, then treating with physostigmine and redetermining the minimal rate of excitation (64). The prolongation of the action of acetylcholine can be determined for different doses of physostigmine. Strong single induction shocks applied to the atria of the turtle's heart will produce first a diminished strength of contraction then, with increasing intensity, a slowing in rate (65). This is attributed to the stimulation of vagal fibers, since it is prevented by atropine and prolonged by physostigmine. It is not clear why the vagal fibers, which are easily stimulated in the nerve trunk, have such a high threshold in the atria.

Acetylcholine in high concentrations may cause first a slowing then an increase in the strength of the contraction of cardiac muscle. The depression in activity can be suppressed by a dose of atropine too small to block the stimulating action. Ergotoxine, however, will block the stimulation by acetylcholine (66). In a more detailed report (67), the possible mechanisms of this epinephrine-like action are considered, but the authors are unable to decide between ganglionic sympathetic structures or chromaffin tissue in the heart or both.

In the elasmobranch heart no sympathetic innervation has been demonstrated, but it is extremely sensitive to epinephrine, a mechanism which may aid in the regulation of the heart otherwise under tonic vagal control (68).

The potentiation of the response of the turtle heart to vagal stimulation or to exogenous acetylcholine by a reduction in pH, is further evidence that endogenous acids may be a part of an integrative system acting upon cholinergic mechanisms (69). Fetter (70) has described a seasonal variation in the threshold of the vagus nerve in the turtle, using the heart as an indicator. Since the action of acetylcholine or vagus stimulation are so greatly influenced by ionic conditions and by temperature, Fetter's results need confirmation with oscillographic recordings from the nerves.

Gregg & Shipley (71) found that stimulation of the stellate ganglia or their branches to the heart increases coronary flow and that the increase is usually greater in the left artery. The changes in coronary flow are dissociated from aortic pressure or heart rate. Later experiments (72) indicate that this increased flow is not due to a specific vasodilator action on the coronary vessels, but is a phenomenon secondary to the increased metabolism of the heart and produced by the local accumulation of metabolites. Freedberg *et al.* (73) have used heat or cold as a stimulus during standardized work to initiate what is thought to be a reflex change in coronary circulation. In a warm room, a patient with angina pectoris can do more work than in the cold. Localized cooling, such as holding ice in the hand, will cause an anginal attack even though the room is warm, but pretreatment of the patient with heat interferes with the response to cold. It is suggested that heat is a coronary dilator, cold a constrictor.

Amann & Scharfer (74) have recorded simultaneously the electrocardiogram, respiration, and action potential of single nerve fibers or the trunk of the cardiac nerves in cats. Activity recorded from a branch of the vagus was increased during atrial systole, then again during ventricular contraction. Other fine branches of the cardiac nerves conducted bursts of impulses synchronized with respiration, but which originated in changes in the circulatory resistance of the lungs. Walsh & Whitteridge (75) recorded the activity of a single fiber in the cervical vagus which responded with seven to eight impulses to each heart beat during inspiration, but with only one to two during expiration. It is possible to imagine that, through this fiber, changes in pulmonary circulation could affect the respiratory center. By similar recordings it was possible to show that cardiac dyspnea does not arise from the excitation of vagal stretch receptors in the lungs (76). Sensory impulses from the great veins, perhaps those giving rise to the Bainbridge reflex,

were also recorded (74). Their records of bursts of activity in the depressor nerve during ventricular systole are very similar to those recorded by Bronk & Stella (77) from the carotid sinus nerve.

The variations in the pattern of the sympathetic innervation to the heart have been illustrated in great detail by Saccomanno (78). The thoracic nerves, which originate as low as the seventh thoracic ganglion in man, contribute approximately twice as many fibers to the cardiac plexus as do the cervical sympathetics. Anesthesia of the stellate ganglion rapidly suppresses extrasystoles (79).

The limulus heart ganglion, composed of many neurons, has a rhythmic discharge which is synchronized with the heart beat (80). However, when the electrical activity of a single neuron is recorded, many discharges of high frequency may occur during a single heart beat. The force which synchronizes all the neurons into phasic activity and which appears in the records as a slow negative potential, is responsible for the increased frequency of discharge of a single unit and for the recruitment of new units during the cyclic bursts of activity.

*Blood vessels.*—Several vasomotor reflexes have been described and analysed within the past few years. Rein (81) has described a new local reflex for maintaining the circulation within the liver. When the liver was eliminated from the dog's circulation, it was observed that ligation of the hepatic artery was followed by a momentary throttling of the celiac and superior mesenteric arteries, and that this response was sharply limited to the intestinal circulation. Further investigation showed that the reflex is entirely independent of other pressoreceptors, that it is reinforced by anoxia, and that it is not abolished by acapnia. The reflex is elicited by a fall in pressure within the hepatic artery, and Rein (82) suggests that it represents a protective mechanism for the blood supply of the liver, rather than one in the interest of the general circulation.

Dipping the face into cold water or blowing cold air on the face causes a generalized vasoconstriction in man (73, 83); sweating, tremor, and increased metabolism are further components of the total reaction, which is considered important in temperature regulation. The reflex is much stronger in rabbits, even when they are under light narcosis (84). König (85) has observed that a lowering of the temperature of the blood initiates reflexes which result in the production of heat. A generalized vasoconstriction is observed after smoking cigarettes; the response is just as great when the

cigarette contains no nicotine (86). It is thought that the reflex originates in irritation of the respiratory tract. Vasoconstriction may occur in the nasal mucosa in response to cooling the skin. There is a rough parallel between changes in nasal and in skin temperature in response to cutaneous chilling and warming (87).

In exercise, hyperthermia, and anoxia the cardiac output increases, but in hyperthermia the heat regulating mechanism usually causes a vasodilation so marked as to interfere with the control of blood pressure (88). Furthermore the polypnea of hyperthermia causes a marked fall in alveolar carbon dioxide tension, especially in anesthetized animals, in which not only the rate but the depth of respiration is increased; this loss of carbon dioxide is a further load upon vasomotor control. However, when dogs were quickly heated in a water bath, there was no fall and often a rise in arterial pressure, despite the extreme decrease in alveolar carbon dioxide tension and a rise in peripheral blood flow. Apparently this procedure resulted in an increased tonus of the vasomotor centers, although the centers showed no greater sensitivity to carbon dioxide.

The volume changes in the finger tip of man have been recorded under a wide variety of conditions and interpreted by correlating the wave form with the carefully controlled conditions of the experiment (89). It is clear that the volume changes originate in the changes of small blood vessels which are controlled by autonomic nerves. Rhythmic fluctuations in volume with a frequency of seven to ten per minute, designated alpha waves, are associated with phasic activity in the autonomic nerves and disappear when the sympathetic nerves are cut or blocked with a local anesthetic. Emotional state is an important though not the sole determinant of the magnitude of the alpha waves. During anxiety, for example, when the autonomic discharges are maximal, the small blood vessels are so constricted that the alpha waves are small. In moderate emotional states the alpha waves are maximal, and in contentment they are again small, approaching the condition seen after sympathectomy. The pulse waves provide a necessary guide in these interpretations. The same procedures have been used in detecting the changes that occur in one peripheral vascular bed when vasodilation is produced in another (90). Simultaneous records from toes and fingers indicate a compensatory vasoconstriction in the toes when the stellate ganglion is paralysed. The reflex vasomotor responses of the paw of the cat have been described (91).

The military injuries of the past few years have necessitated as



well as provided opportunity for studying the behavior of denervated blood vessels. The degree of denervation ranges from the minimal, caused by damage to the cerebral cortex (92), to the maximal which results from transection of a peripheral nerve (93). Intermediate, and in ascending scale of severity, are disturbances caused by lesions of the brain stem or spinal cord, by preganglionic or by ganglionic sympathectomy. Sensitization is not restricted to smooth muscle or to the postganglionic nerve cell, or even to the preganglionic neuron within the spinal cord, but extends, in diminishing intensity, up to cortical levels. Complete denervation of a hand or digit produces vasomotor disturbances similar to those caused by postganglionic sympathectomy, in that local cooling or epinephrine leads to marked constriction (93). The effects differ in that the disuse of the denervated tissue results in a lower temperature, which may also be affected by the normal heat loss in immediately adjacent areas. Richards (94), who also studied vascular reactions in denervated digits, concluded that the slow and incomplete reactions of the affected fingers were caused by the liberation of substances in the normally innervated blood vessels of adjacent parts. This applies to vasodilation as well as constriction, and reflex dilation in normal skin adjacent to a denervated finger will be followed by partial dilation in the affected finger.

Doupe (95) believes that denervation attended by nerve degeneration (postganglionic) differs from that in which the innervation remains intact (preganglionic). The smooth muscle of the blood vessels "accommodates" rapidly to injected epinephrine if its nerve supply remains anatomically intact, even though paralysed by preganglionic section. When the nerve supply degenerates, the muscle not only becomes hypersensitive to epinephrine, but gives a longer lasting response; preganglionic denervation causes only a lowering of the epinephrine threshold. By comparing simultaneous vasomotor reactions in normal and denervated digits, Doupe was able to show a reflex dissociation of neurogenic vasoconstriction and epinephrine secretion. In hyperglycemia, for example, vasodilation may occur in the normally innervated hand, while vasoconstriction in the denervated one indicates a liberation of epinephrine. The denervated hand or finger provided a means of assaying the amount of epinephrine liberated in response to various stimuli. It was estimated that the rate of secretion could be elevated by reflex excitation to 2.0 to 6.0  $\mu\text{g. per min.}$

A clear distinction must be made between the behavior of blood

vessels in the skin of distal parts of the extremities and the vasomotor activity in the cutaneous areas of proximal parts. It is reported that stimulation of the cutaneous sympathetic nerves of the arm or leg causes vasodilation, which is independent of sweating, while in the fingers or toes the response is marked vasoconstriction (96). The vascular response to inflammation is not dependent upon the nerve supply to the tissue (97).

Sensitization to epinephrine by postganglionic sympathectomy lasts, in the blood vessels of the dog, for as long as ten years, and during this time there is an hypertrophy of the muscular coat of the arteriolar walls (98). However, observations in the same laboratory on the blood vessels seen in transparent chambers inserted in rabbit's ears include cases of loss of hypersensitivity to epinephrine and return of the arteriolar diameters to normal when regeneration of the sympathetic nerves could not be demonstrated. Denervation which caused an increased sensitivity to epinephrine did not alter the threshold of the blood vessels to ergotoxine, ephedrine, or pitressin, but did diminish or abolish the tachyphylaxis to the last two drugs (99).

Sympathectomy, especially when extensive, causes a redistribution of the circulating blood so that the fingers, which are normally warmer than the toes, may become colder (100). Furthermore, vasomotor reflexes, which adjust the distribution of blood in response to posture, may be so impaired by sympathectomy that sudden changes in position may be disastrous (101, 102, 103). Perhaps the most important loss in vasomotor regulation occurs in the arteriolar end of the capillary, for the normal pressure gradient in this zone is greatly diminished (104).

Morphine in some way reduces the activity of the sympathetic nervous system, according to Himmelsbach (105), for an increase in blood flow to the hand after the administration of morphine depends upon intact sympathetic control. This effect is quite different from the central action of morphine on the antidiuretic system described by de Bodo (106) and on the blood sugar regulating mechanism described by Brooks *et al.* (107). The local application of heat can also cause a great increase in blood flow; in the forearm the values range from 0.5 cc. per 100 cc. of tissue at 13°C. to 17.6 cc. at 45°C. (108). Increasing room temperature increases the blood flow of a hand immersed in water; on the other hand, as the water temperature is lowered, the flow decreases until a minimum

is reached at 10°C. (109). The rise below this temperature may be caused by paralysis of the vasoconstrictor apparatus. The reflex dilation of cutaneous blood vessels in response to heat may fall far short of the maximal: the dilation produced by mecholyt iontophoresis may be twice as great as that obtained reflexly (110). The tonic vasoconstrictor action of the sympathetic nerves to the blood vessels of skeletal muscle has been clearly demonstrated by recording the volume of the forearm before and after blocking the nerves to that region. The participation of the cutaneous blood vessels in the increase in volume was eliminated by producing in them a maximal constriction by the electrophoresis of epinephrine (111).

The importance of dorsal spinal roots in reflex vasodilation has been emphasized by the experiments of Bach (112). Doupe (113) has taken advantage of an anomalous innervation of the muscles of the ulnar side of the hand by the median nerve to demonstrate a vasodilation which could be explained as axonal in nature, although the axons involved are not sensory, since the ulnar nerve was severed below the elbow. It is assumed that these motor fibers liberated, near their terminations, vasodilators which affected the overlying cutaneous vessels. The response of denervated blood vessels to acetylcholine is greater and more prolonged when the alveolar carbon dioxide tension is diminished (114).

A quantitative expression of vasomotor tone devised by Green *et al.* (115, 116) requires the comparison of arteriovenous pressure differences necessary in the experimental and in control conditions to produce the same rate of blood flow. After transection of the spinal cord at T<sub>1</sub>, the fall in blood pressure is largely due to a reduction in peripheral resistance (117). Compensatory vasoconstriction in the normally innervated vessels is important in preventing a further fall in peripheral resistance (118). After spinal anesthesia, the blood vessels of the toes are dilated, those of the fingers constricted. Ephedrine, under these conditions, affects only the vessels with a functional innervation.

An increased capillary permeability as the result of sympathetic activity or epinephrine secretion (119 to 122) has led Engel (123) to recommend sympathetic block for the treatment of traumatic shock. Lindner *et al.* (124) were unable to demonstrate any substance in lymph collected during shock which affected capillary permeability. Eversole *et al.* (125) recognized the importance of sensory impulses from the traumatized region in producing shock,

but thought it improbable that this factor alone was sufficient to cause death; loss of blood into the traumatized tissue is also important. Post-traumatic reduction in bleeding time appears despite sympathectomy (126), and reflex changes in the tone of the blood vessels are not a contributory factor; changes in blood chemistry play an essential role in the origin of post-traumatic reduction in bleeding time.

The sensory innervation of blood vessels makes up a coarse irregular plexus in the adventitia (127). Destruction of the spinal cord and sensory ganglia from  $T_6$  caudad in the rat causes this plexus on the pelvic arteries to degenerate, leaving only the post-ganglionic sympathetic nerve supply to the smooth muscle of the media. Such a sensory plexus may be concerned in the circulatory collapse that occurs in man as the result of mechanical stimulation of the arterial wall (128).

The importance of afferent impulses in the production of shock is denied by Phemister and his associates (129, 130, 131). They conclude that the inability to produce more than a brief lowering of the arterial pressure by stimulation of somatic nerves and the comparatively short duration of the periods of low blood pressure during syncope, make it doubtful that primary shock is ever produced in man by the action of afferent depressor nerve impulses. They have further shown that prolonged periods of low blood pressure produced by stimulation of the depressor nerve are quickly terminated on cessation of stimulation. Audiogenic stimulation of rats causes a response similar to an autonomic epilepsy, and the animals frequently develop hypertension (132). While the authors emphasize that their observations do not prove the neurogenic origin of hypertension, they do consider them valuable evidence that nervous stimulation is associated with the production of hypertension. Maling (133) has shown that, despite a sustained low pressure during prolonged depressor nerve stimulation, there is a fatigue of the reflex. This fatigue is demonstrated by the progressive increase in pressor reflexes. There seems to be no fatigue of the pressor reflexes freed from inhibition by section of the moderator nerves (134, 135); marked hypertension persisted as long as five years. There is, furthermore, no evidence that any humoral mechanism is responsible for this chronic hypertension; it is essentially reflex. Bing has presented as evidence of a generally increased sympathetic tone, the constriction of the afferent arterioles of the renal glo-

meruli, accelerated circulation in the extremities, and a rise in cardiac output (136). Peculiarly enough, this increased sympathetic activity, although adequate to produce a severe hypertension, is not sufficiently great to interfere with pressor responses to epinephrine (137). The greater responsiveness of the pressor reflexes in hypertension, reported by some, is not due to the higher basal pressure; in normal subjects as the pressure is systematically raised, the pressor response to a standard stimulus is progressively diminished (138). The effects of 833 F and 933 F on the blood pressure depend not only upon the route of administration of the drug, but also upon other agents modifying the pressure. It is possible, with the use of these drugs, to make a differential diagnosis between renal hypertension, which is humoral in origin, and neurogenic hypertension, which is essentially a state of vasopressor hyperreflexia (139).

Lambert & Wakerlin (140) find that section of the carotid sinus and aortic nerves causes a lability of the blood pressure rather than a hypertension; that the pressure, as recorded from arterial puncture, falls progressively on successive punctures; and that when the readings were taken in a quiet room, they were much lower than when made in a disturbing environment.

The cytology of the carotid body has been thoroughly reinvestigated by Hollinshead (141), who has employed a great variety of techniques. Since neither Nissl granules nor neurofibrils could be demonstrated in the parenchymatous cells, he concludes that they are not related to neurons. The presence of granules, probably secretory, led him to suggest that chemoreflexes might be initiated by the release of some substance from these cells. This is supported by the disappearance of these granules during severe anoxia (142). Hollinshead & Sawyer (143) do not believe that the chemical transmitter between these chemoreceptor cells and the sensory nerve fibers is acetylcholine, because the cholinesterase content of the organ is extremely low. While it may not be relevant, the observation of Armstrong (9) that the concentration of the esterase in cholinergic systems varies between wide extremes is brought to mind.

The thoracolumbar outflow of the autonomic system is the only efferent pathway for vasomotor reflexes arising in the carotid body (144) and involving the vessels of both somatic and visceral organs (145).

The application of pressure over the carotid sinus area in man causes an hyperpnea which can be separated from the vasomotor response during the recovery from procaine block; the respiratory response returned before the vascular reflex (146). Pressure may affect the respiration by interfering with the blood supply to the carotid body. In a far more comprehensive paper, Dripps & Comroe (147) have reviewed the clinical significance of the carotid and aortic bodies.

The pressoreceptor area related to the carotid sinus in the cat includes not only the beginning of the internal carotid, but part of the occipital artery (148). The limits were determined by a characteristic elastic tissue arrangement and it would be interesting to compare these results with those obtained by determining the distribution of the specific pressoreceptor nerve endings. The excision of this area in the dog causes an acidosis (149), explained only in part by the depressed respiration; there is an elevation of fixed acids in the blood and an increase in oxidative metabolism.

Hyperglycemia which develops after severe hemorrhage is not a result of the anoxia and probably not caused by the reflex liberation of epinephrine; it differs from epinephrine hyperglycemia in that the latter is dependent upon nervous mechanisms associated with the carotid sinus or the vertebral arteries (150).

A comprehensive review of cerebral circulation (151 to 154) relieves us of a consideration of that subject save for two papers. Spiegel *et al.* (155) have shown that the slowing of cerebral blood flow induced by labyrinthine stimulation is secondary to a generalized fall in blood pressure and is without local significance. The electrical activity (EEG) of the brain is modified through a cholinergic system which may act directly on the cerebral blood vessels or upon cerebral metabolism (156).

Several studies of the peculiarities of the nerve supply to specialized regions of the vascular system require comment. Spivack (157) has shown that the umbilical vessels of man and the guinea pig are free of nerves; Acevedo (158) has shown that there is some motor control of the thoracic duct, and Papper & Imler (159) have suggestive evidence of sympathetic control of the leg veins in man. They observed a dilation of the veins after sympathectomy and thought the result was accomplished by a diminution in venous tone (159). An alternative interpretation is that sympathectomy permitted a transmission of arterial pressure through the dilated capillaries to the distensible veins (104).



*Sweat glands.*—The majority of the investigations of sweating which have been reported in the past few years have been concerned primarily with the diagnosis of central and peripheral nerve lesions. Sweating is an especially satisfactory indicator of partial or complete sympathectomy, since it is controlled by cholinergic innervation and therefore influenced little if at all by substances released into the blood stream. Furthermore, denervated sweat glands show no atrophic changes, and, unlike most secretory tissues, show little spontaneous activity (160). This advantage, that reflex sweating indicates the arrival of nervous impulses at the gland responding, has been profitably exploited by several techniques. Whelan & Richter (161) have described recent improvements in the apparatus and procedures for measuring electrical skin resistance. One of the great advantages of this technique is that it does not require the cooperation of the patient, and as a purely objective procedure, it can be used in shock, malingering, or disorientation (162). With this technique, Richter has mapped the rate of sweating in various skin areas of normal subjects under conditions of controlled environmental temperature and during sleep (163). The areas of low electrical resistance contract in cold and during sleep; they expand on waking, during exercise and excitement, or in a warm room. These areas, which do not conform to the distribution of the peripheral nerves, are the projections of central patterns of sympathetic representation. Changes in skin resistance have been used in determining the preganglionic outflow to the sweat glands of the hand in man (164) and in determining the threshold to pain (165).

Silverman & Powell (166) have measured palmar sweating by a reasonably quantitative technique which also provides permanent records. The palms are painted with a solution of ferric chloride, dried, and placed in contact for three minutes with dried paper previously soaked in tannic acid. Sweat, by bringing the two substances into solution, permits the formation of the black ferric tannate, whose density is proportional to the amount of sweat secreted.

Neumann *et al.* (167) have measured sweating by a highly accurate method: the water secreted onto a cat's pad in a given time is weighed. The pad is enclosed in an airtight vessel through which dry oxygen is passed; the moisture thus removed from the pad by evaporation is condensed in a cold coil which can be detached for weighing. After crushing the nerves to the foot, regeneration is



more rapid and more complete than after transection and suture. For ten to thirty weeks after the appearance of the first sign of function, sweating increases steadily until 40 to 70 per cent of the normal rate is restored.

Reflex sweating may be elicited through the spinal cord isolated by complete transection (168). The lower level of thermoregulatory sweating and the upper level of this spinal reflex sweating may be used to study the spinal segmental innervation of the sweat glands. The dermatomes for sweating are much larger and have a much greater overlap than the sensory dermatomes. Ray *et al.* (164) have shown that in man as many as seven spinal segments may contribute to the innervation of the sweat glands in the finger. It is highly probable that most of this overlap is due to convergence, within the chain ganglia, of many preganglionic fibers onto a single post-ganglionic neuron.

The representation of sweating within the cerebral cortex is clearly demonstrated in a case reported by Bucy (169) in which localized sweating was part of a localized convulsive seizure. The somatic seizure was limited to the face, while the area of sweating was more extensive, including the neck, arm, and axilla. Fisher & Stavrakys (92) noted that, when mecholyl was injected into patients with frontal lobe lesions, sweating was diminished on the extremities of the opposite side. This reaction was most prominent when the lesion involved the premotor or motor cortex. These cases illustrate an additional principle, that of sensitization by denervation above the preganglionic level. When pilocarpine or mecholyl were injected, sweating was more profuse over the affected area than in the rest of the skin. These drugs produce disagreeable side reactions; furmethide, however, produces none, and also more regularly causes sweating (170).

Nerve block produces a paralysis of the sweat glands, and the affected area is easily distinguished by its increased electrical resistance (162) or the absence of thermoregulatory sweating. Highet (171) has used procaine block in estimating the degree of peripheral nerve lesions, and in studying the role of the autonomic nerves in post-traumatic causalgia. Barcroft *et al.* (111) have completely suppressed sweating by the electrophoresis of epinephrine, but this paralysis is almost certainly due to a complete arrest of cutaneous circulation.

*Sebaceous glands.*—Sebaceous secretion, unlike sweating, con-

tinues unaltered after sympathectomy in man (172), but there is some clinical evidence that it is influenced through sympathetic innervation (173).

*Pituitary.*—The supraopticohypophyseal system seems to be established as an autonomic effector, comparable in innervation and function to the adrenal medulla. The gradual acceptance of the idea that the control of diuresis is the only physiological rôle of the neurohypophysis has led to the design of experiments in which this easily elicited activity is used as the indicator of pituitary stimulation. Furthermore, the anatomical features of the supraopticohypophyseal system are now widely known and provide some basis for interpreting current physiological observations. The nerve fibers which descend from the supraoptic nuclei into the neurohypophysis apparently constitute the efferent limb of a reflex arc which can be activated by cutaneous (174) or deep (175) stimuli. Removal of the neurohypophysis (174) or transection of its stalk (175) prevent the antidiuresis which these painful stimuli normally cause. O'Conner & Verney (176) have discovered that the antidiuresis produced by faradic stimulation of the skin or emotional stress is of two types: a rapid one, abolished by interruption of the sympathetic fibers to the adrenal and kidney, and a slow one, dependent upon the release of an antidiuretic from the neurohypophysis. In a normal dog the responses may alternate or be mixed. The irregular appearance of the slow pituitrin response is attributed to the increased sympathetic activity during emotional stress, which somehow interferes with the liberation of pituitrin.

Dehydration also releases pituitrin (177), and failure of patients to concentrate the urine above a specific gravity of 1.010 when drinking water is withheld, has been proposed as evidence of a nonfunctional posterior pituitary (178). Hypertonic sodium chloride solutions by intravenous injection are perhaps even more effective in liberating pituitrin into the blood stream, and have been used both clinically (179) and experimentally (180) in testing the functional integrity of the supraopticohypophyseal system. Since both dehydration and the administration of hypertonic salt solutions elevate the osmotic pressure of the plasma, it has been suggested that this change, whether caused by urea, sodium sulphate, or sodium chloride, is the effective stimulus to the release of pituitrin (180). Exercise produces an antidiuresis which is thought to be mediated through the pituitary (181).

The liberation of pituitrin is perhaps more conveniently detected by applying the test stimulus during the course of a standardized and reproducible water diuresis than under any other conditions. Since the pituitrin in the blood stream is short lived, the antidiuresis is correspondingly brief, lasting only twenty to fifty minutes after the injection of doses just above threshold, or after painful stimulation of the skin (174). The time course of such an antidiuresis could hardly be followed by the hourly collection of urine as practised by Boyd *et al.* (182) in studying the release of pituitrin in response to flashing a light into the eyes of rats. In the absence of a satisfactory inhibition of water diuresis in the hydrated rat, they resorted to the diuretic action of pituitrin, which is obtained only with large doses of the hormone. With this indicator, they obtained evidence of pituitrin release in response to retinal stimulation, and assays of the neurohypophysis from the stimulated rats reveal a marked loss in pituitrin content.

A variety of drugs will also interrupt the normal course of a water diuresis in normal but not in hypophysectomized animals. Pickford (183) has shown that acetylcholine injected into atropinized dogs has an antidiuretic action only in the presence of the pituitary, and attributes the response to the "nicotine" effect. Burn *et al.* (184) found that nicotine itself was antidiuretic in action if the pituitary was intact. Yohimbine (185) and morphine (106) have similar actions. The authors are practically unanimous in assuming that the particular agent which they employ, whether salt or drug, acts directly upon the supraoptic neurons to initiate activity which is transmitted down the hypophyseal stalk to the pars nervosa. They are all impressed by the extreme vascularity of the supraoptic nuclei (186, 187) and readily attribute to these neurons the dual rôle of chemoreceptor and efferent path to the pituitary. Actually none has any evidence that anything of the sort occurs. They have abolished the antidiuretic response by cutting the pituitary stalk, which may be the final common pathway through which several systems regulate pituitrin secretion; or they have, by hypophysectomy, excised the effector organ. The chemoreceptors responsive to changes in osmotic pressure, to morphine, or to acetylcholine, may be as remote from the hypophysis as the aortic body from the respiratory center of the medulla. Animals with an island of hypothalamic tissue overlying the intact pituitary, such as those used by Sumwalt *et al.* (188), could be used to

great advantage in delimiting the integrative level of these pituitary reflexes.

A third function has been attributed to the supraoptic neurons: the secretion of an antidiuretic hormone. Gaupp & Scharrer (189) several years ago introduced the idea, supported only by histological evidence, that granules in the cells of the paraventricular and supraoptic nuclei indicated the production of a hormone concerned with the regulation of urine flow. More recently in a review, Scharrer & Scharrer (190) have collected their comparative studies on the diencephalic cells which have the cytological characteristics of secretory tissue. The neurosecretory material in these nerve cells is inversely proportional to the Nissl substance (191). Palay (192) describes the production of secretory granules within the nuclei of diencephalic neurons in fishes, a process which also takes place in the cells of the pars nervosa of man (193). But in the catfish these acidophilic hyaline granules are found only in the preoptic nucleus, which is the nucleus of origin of the tractus preopticohypophysius, and along the axis cylinders which enter the pituitary (194). Palay suggests that the neurosecretory products, originating within the nuclei of the preoptic cells, migrate toward the neurohypophysis and are directed toward their destination by the axis cylinders of the tractus preopticohypophysius. These ideas have been projected far beyond their supporting physiological evidence. Melville & Hare (195) have demonstrated that the supraoptic region of the hypothalamus of the dog contains 10 to 30 per cent as much antidiuretic hormone as the pars nervosa of the pituitary, and that this material is probably localized in the supraoptic neurons, since their degeneration, as the result of pituitary stalk section, is attended by a disappearance of the hormone. These limited experiments show only that the hormone is present in the supraoptic nucleus and give no clue to its origin, to its distribution, or to its part in the control of water exchange.

Occasionally some evidence appears that the pituitary releases, in response to severe stimulation, enough pituitrin to elevate the arterial pressure. Olson & Necheles (196) found that thermal trauma, which caused a pressor response in the normal dog or cat, produced a fall in blood pressure in hypophysectomized animals. Although removal of the spleen, adrenals, or the splanchnic nerves did not alter the pressor reflex, while hypophysectomy did, they recognized that the pituitrin, the pressor dose of which is several

hundred times the antidiuretic dose, was only one of the factors concerned in the pressor response.

The origin of the pituicytes from the ependyma has been described in the chick (197), pig (198), and man (199). While mitotic figures are common in the early stages of differentiation (198), they are very rarely seen in the adult (200, 201, 202). The prolonged administration of salt leads to at least a fifteen-fold increase in the number of mitotic figures and to a marked depletion of the pituitrin content of the gland (202).

The supraoptic nucleus of each side contains about 8,500 cells in the rat, 46,000 in the dog, and 67,000 in man (203). There are, of course, other hypothalamic contributions to the innervation of the pars nervosa, which, according to Shanklin (204), contains nerve cells itself.

Since innervation of the pars anterior by hypothalamic fibers would provide the anatomical basis for the effects of light upon the cyclic activity of the gland and upon the rate of maturation of the reproductive tract in immature animals, there is a sustained enquiry into its nerve supply. Truscott (205) describes for the rat a far more generous innervation of the pars anterior by hypothalamic fibers than is usually seen, and estimates the total number of fibers to be about 1,500. His observations contrast with those of Drager (206) who reports that most of the nerves seen in the anterior lobe are autonomic in origin, and that only an occasional aberrant fiber is contributed by the hypophyseal stalk. No hypothalamic-hypophyseal nerves were found in the pars distalis of the bird, in which gonadal activity is especially responsive to light stimuli, in spite of the fact that the infundibular process and the pars distalis are completely separate. Removal of one eye from adult pigeons produced no degeneration of myelinated fibers which could be traced into the pituitary (207), but the possibility of indirect connections remains. Lamoreux (208) considers temperature more important than light in influencing comb growth in Leghorn cockerels. Prolonged alternate periods of light and darkness did not affect the estrous cycle of adult cotton rats, but darkness did retard the development of the reproductive tract in the immature animals (209).

Studies from Ranson's laboratory on the hypothalamic control of the sexual cycle of the guinea pig (210 to 213) reveal two sharply distinguished effects of localized lesions. Large lesions caudal to the

optic chiasm produce estrus, although mating behavior is abolished, since the lesion interferes with the nervous integration of mating reflexes: lesions in the median eminence produce diestrus. It is suggested that the influence of the median eminence upon the gonadotropic activity of the pituitary is mediated through a humoral mechanism, rather than by fibers passing from the hypothalamus to the anterior lobe.

*Thyroid.*—The elevation of the metabolic rate which occurs in response to cold, disappears after thyroidectomy, but not immediately. Furthermore, the injection of thyroxine restores the response. Gergeley (214) concludes that it is not necessary to have an active thyroid which reacts at the instant of cold stimulation by an increased secretion for the thyroid gland to participate in heat regulation.

*Kidney.*—The kidneys and the sweat glands lie at the extremes of the scale as far as the effects of sympathectomy are concerned. The latter are almost wholly paralysed, while no significant change in any phase of renal function is caused by the most intensive denervations. Sympathectomy in dogs is reported to produce a renal vasodilation (215). This effect was observed a few hours after operation by noting on histological examination the quantity and distribution of Berlin Blue injected in a gelatin solution before fixation of the tissues. It should be remembered that functional studies, in which chemical methods of measuring renal blood flow were used, showed no renal hyperemia as a result of interference with the nerve supply to the kidney of the dog (216) or of man (217, 218). Talbot *et al.* (219) studied the effects of sympathectomy on kidney function in hypertensive patients from whom a renal biopsy specimen was obtained during the operation. Extensive bilateral splanchnicectomies had little effect on glomerular filtration or renal blood flow, but appeared to have halted the progress of the renal vascular disease. No significant increase in renal blood flow in patients was observed on increasing the room temperature, although peripheral blood flow was greatly elevated (220).

Although diminution or abolition of sympathetic innervation to the kidney does not increase renal blood flow or glomerular filtration, sympathetic stimulation or the administration of sympathomimetic drugs produces marked effects on the renal circulation. Ranges & Bradley (221) found that epinephrine and paredrinal decreased renal plasma flow but increased the filtration fraction

sufficiently to maintain a constant rate of glomerular filtration. This response suggests a constriction of the efferent arterioles. Their observations, made on man, find an almost exact counterpart in those of Forster (222) on the frog with small doses of epinephrine. However, when larger doses were used, renal plasma flow, glomerular filtration, and, significantly, the filtration fraction, were all reduced. This pattern of response, together with a diminution in the number of functional glomeruli, suggests constriction of the afferent arterioles. Forster points out the significance of this response in the frog, in which water exchange is regulated by changes in the quantity of glomerular filtration, rather than by variations in the rate of renal tubular reabsorption of water, which is the regulatory mechanism in most mammals.

Corcoran & Page (223) observed an oliguria in dogs under pentobarbital anesthesia, and on investigation found it to be associated with a depression in diodrast and inulin clearances. Again the response is explicable by constriction of the afferent arterioles and is attributed to the hypertensive effect of pentobarbital. Craig *et al.* (224) made the same observations on animals under ether or cyclopropane anesthesia, and added the observation that the glucose  $T_m$  was also depressed. This may indicate a diminution in the number of functional nephrons as observed by Forster (222) in the frog's kidney following the administration of large doses of epinephrine. These effects, obtained only in deep anesthesia, are considered the results of neurogenic renal vasoconstriction. Similar experiments in which each ureter is catheterized, performed after unilateral sympathectomy, should reveal the relative importance of nervous and humoral agencies.

The renal nerves are not solely responsible for the disturbances in renal function which accompany the onset of shock produced by tourniquets which partially occlude the circulation in the limbs; some humoral agent is apparently involved (225). The possibility of the direct intervention of nervous regulation in glomerular function is strengthened by the anatomical demonstration of nerves to the glomerular apparatus (226).

#### REFLEX MECHANISMS

*Spinal reflexes.*—In addition to new descriptions of established spinal reflexes (168), two original observations on spinal activity have appeared. Groat & Peele (227) recorded a large rise in arterial



pressure when mechanical pressure was applied to the spinal cord of functionally decapitate cats. One may suggest, from experiments of Alexander (228), that anoxia of the compressed cord could account for the pressor response. Alexander isolated the upper thoracic portion of the cat spinal cord by combining low cervical and mid thoracic cord transection with bilateral section of the dorsal spinal roots between the cord lesions, and by bilateral section of the sympathetic trunks above and below the levels of outflow of this deafferented cord segment. An elevation in the blood pressure, or clamping of the aorta at the level of the diaphragm, diminished the tonic activity of the cardiac nerve; anoxia, on the other hand, greatly increased the tonic activity. It is clear that the elevation in blood pressure is effective in diminishing the tonic activity through affording a better blood supply to the spinal cord. Bernthal & Woodcock (229) have also noted the direct action of hypoxia on vasomotor activity; a small decrease in oxygen affects reflex activity, while a much greater hypoxia affects directly the vasomotor center, producing what is termed "centrogenic vasoconstriction." When the blood supply to the brain is sufficiently restricted by ligation of the carotids, the respiratory response to hypercapnia and the vasomotor response to anoxia are increased (230). Since these increases persist after denervation of the sino-aortic areas and vagotomy, it seems that the anoxia acts directly upon the centers. Without localizing the site of action, Grandpierre (231) also noted an increase in sympathetic reflex activity when the partial pressure of oxygen in the inspired air was lowered beneath its normal value. For a more detailed description of the effects of anoxia on reflex activity, the writings of Gellhorn are suggested (232, 233, 234).

The capacity for heat regulation which appears three to four days after complete transection of the lower cervical cord, is abolished by even light anesthesia, but is not affected by removal of the lumbar cord (235). Since the stimulus was applied to a hind leg and the response observed in the same limb, the spinal mechanism is clearly not responsible. Since an increase in metabolism appears in one leg only when the other is so energetically cooled that the rectal temperature falls  $0.5^{\circ}$  to  $1.0^{\circ}\text{C}.$ , it is possible that the cooled blood affects the intact centers rostral to the transection.

*Bulbar reflexes.*—In contrast to the pressor response obtained

by Groat & Peele (227) from pressure on the spinal cord of cats without an encephalon, the arterial hypertension which is elicited by increased intracranial pressure is dependent upon the medulla (236).

While we have been indoctrinated for years with the concept of a widespread generalized reflex activity of the sympathetic nervous system, we should not reject the evidence of differential responses in sympathetic reflexes. For example, thermoregulatory sweating occurs when cutaneous vasoconstriction is inhibited; pilo-erection may occur when sweating is suppressed; in hypoglycemia, epinephrine may be secreted when the cutaneous vessels are dilated (95). This requires that we admit the existence of some local representation within the peripheral ganglia of these various effector organs. The pattern of this representation in the ganglia is completely unknown, but within the central nervous system two important facts are now clear: the afferent path for the autonomic reflex may be anatomically distinct from the afferent path subserving sensation (3), and the efferent paths for each sympathetic effector are also separate, so that a lesion may interfere with one function without affecting the other (237). For the first of these, we are indebted to Harris, Hodes & Magoun (3), who found that impulses originating in painful stimulation of a sensory nerve reached the third nerve nucleus by ascending through the central gray of the mesencephalon, while those to the thalamus pass along the spinothalamic tract. Furthermore, removal of the thalamus did not abolish the pupillary reflex. While it has been known for twenty years (238) that the fibers to the oculomotor nucleus lay in the central gray, the significance of this anatomical fact has been realized only recently (3). Separation of the tracts regulating different autonomic functions was accomplished not by systematic experimentation, but by vascular accidents in the medulla (237).

*Hypothalamic reflexes.*—The hypothalamus, in the course of this review, will be considered the integrative center of the mechanisms regulating energy exchanges. The maintenance of a constant body temperature is managed through three interrelated but distinct nervous mechanisms, controlling respectively heat loss, heat conservation, and heat production. When lesions are made in the anterior region of the hypothalamus in the monkey, one of these mechanisms, that regulating heat loss, is paralyzed so that body temperature rises. During the rise in temperature there is no sweat-

ing, the extremities are cold, and there is intermittent piloerection and shivering (239). The administration of soluble pentobarbital causes a marked fall in body temperature, a relaxation of the piloerection, a large elevation of the temperature of the extremities, and a cessation of shivering. The interruption of the hyperthermia is attributed to a suppression of the heat conservation system, with a cutaneous vasodilation and relaxation of the piloerection, and to a further suppression of heat production, as evidenced by the cessation of shivering. Pentobarbital failed, however, to control the hyperthermia in a case of chronic epilepsy (240). The patient was so dehydrated from vomiting that his heat loss was limited by the increased concentration and viscosity of the blood, rather than by the tonus of cutaneous blood vessels. The localization of the heat loss mechanism in the anterior part of the hypothalamus, or even as far rostrally as the preoptic area, is fairly well established in the cat and monkey. Beaton & Herrmann (241) have reported a war casualty whose wound extended down between the optic chiasm and the anterior commissure, but which did not involve the tuberal region. The man died with a temperature of 108.2°F. nine hours after being wounded. Anterior and anterolateral lesions suppressed the sweating of an aspirin antipyresis (242, 243) as well as that resulting from a fever or high room temperature. Furthermore, these lesions produced a hypo- rather than a hyperthermia, as has been described in the preceding papers (239, 241). Stoll (244) observed a complete loss of heat regulation after bilateral electrolytic lesions in the anterior and middle hypothalamus. In two cases this poikilothermia was preceded by marked hyperthermia. When the reflexes which govern heat regulation are intact, exposure to cold causes an increase in metabolism and a gain in intracellular fluid throughout the body. If the central nervous system is chilled to the point at which general muscular relaxation occurs, these responses are abolished (245).

Obesity, indicating the storage of energy, has long been associated with lesions in the vicinity of the hypothalamus or pituitary body, but the exact site of the causal lesion has never been firmly established. Experimental obesity in the dog is reported to be intimately related to pituitary and adrenal cortical functions; removal of the pars distalis of the pituitary causes a slowly progressive and eventually marked obesity in the adult (246). Hetherington (247) has shown not only that a lesion of the pituitary is not re-

sponsible for obesity, but that hypothalamic lesions will produce obesity in hypophysectomized rats. Rats that showed no significant weight change for eleven weeks after removal of the pituitary, began to gain weight rapidly three to four weeks after lesions were placed, from above, in the hypothalamus with the Horsley-Clarke instrument. He concludes: "Since neither total nor partial hypophysectomy produced adiposity, or prevented its appearance after hypothalamic damage is done, it is not likely that the hypophysis is involved in the production of obesity often associated with injury to structures in the pituitary region. Hypothalamic disorder appears to be the sole factor."

The lesions most effective in increasing fat storage are those which damage or destroy the ventromedial hypothalamic nucleus bilaterally. Since the cells of this nucleus lie intermingled with descending fibers, lesions confined to the limits of the nucleus produce degeneration of neurons in more rostral centers. Hetherington (248) has shown that obesity does not result from these more remote changes. Extensive lesions of the basal forebrain or, in two rats, destruction of the paraventricular nuclei, caused no increase in the deposition of fat. In the same paper, he reviewed the protocols and sections from Ranson's series of monkeys with hypothalamic lesions, and reported that the lesions which produced obesity in the monkey are comparable to those having the same effect in rats.

According to Broebeck *et al.* (249), rats with hypothalamic damage get fat because they eat so much, and it seems generally true that many apparent changes in metabolism as a result of hypothalamic damage are really changes in dietary habits. Immediately on emergence from the anesthesia, the rats eat ravenously, and there is a high correlation between their food intake and their weight gain. These rats showed normal weight gain when pair-fed, but when allowed unlimited food, they became obese. There is little evidence of a qualitative disturbance of fat metabolism and certainly none of an inability to oxidize fats, for when fasted as long as twenty-seven days, they utilized their body fats at rates, on an energy basis, equivalent to their previous caloric intake.

Normal rats eat about 70 per cent of their daily rations at night, but following hypothalamic lesions of the type that cause obesity, they reversed their diurnal pattern of eating, taking 65 per cent of their food during the day (250). These rats were voracious.

cious eaters, and a few days after operation, they would eat a meal of three to four times normal size. Such a voracious appetite has frequently been observed after lesions in the brain stem, but Brügger (251) made the same observation after stimulation of the hypothalamus after the technique of Hess. Since in his experiments the episodes of bulimia lasted only a few seconds to twenty minutes after stimulation, and since others have produced a lasting hunger with lesions, it is suspected that his low-frequency, damped stimulus, by producing sublethal damage to the neurons, caused in them a temporary paralysis. The electrodes, in Brügger's experiments, were located in the vicinity of the mammillothalamic tracts, between the periventricular nuclei and the lateral hypothalamus, and apparently dorsal and caudal to the ventromedial hypothalamic nuclei.

As is suggested above, obesity seems to result from a change in the animal's behavior after hypothalamic damage. Wheatley (252), in an extensive report of personality changes in cats after hypothalamic lesions, related aggressiveness and increased appetite to lesions of the ventromedial hypothalamic nuclei. While his study was primarily concerned with behavior, he made the incidental observation that the greedy cats got fat. Hetherington (247), whose chief interest was in obesity, noticed that his rats that became obese became irritable and unmanageable. Brügger (251) also noted that voracity and an affective defense reaction were associated.

An increased deposition of fat also results from bilateral destruction or retrograde degeneration of the paraventricular nuclei in the dog (246). In evaluating this localization, one should keep in mind that these nuclei were destroyed bilaterally in control experiments on rats without producing obesity (248). Heinbecker *et al.* (246) conclude that changes in metabolism leading to obesity are quantitative rather than qualitative, but consider the effector mechanism to be a complex hormonal one. According to them: "It seems probable that the fibers which pass caudally from the paraventricular nucleus innervate cells within the brain stem which secrete a hormone which directly or indirectly influences the adrenal cortex or the basophil cells of the hypophysis."

One qualitative change in metabolism that is observed after bilateral symmetrical hypothalamic lesions producing obesity, is an abnormally large elevation of the respiratory quotient after the administration of glucose (253). This abnormality appears to be the

result of feeding habits rather than directly due to the hypothalamic lesions. Normal rats, trained to eat their day's ration in three hours or less, show the same increase in the respiratory quotient in response to glucose, although Brooks (254) has observed this marked elevation in respiratory quotient in rats in which periodic engorgement with food had never occurred.

The effect of hypothalamic lesions on pancreatic diabetes is far from clear. Brobeck *et al.* (255) reported that on making bilateral lesions they detected no amelioration of the glycosuria produced by partial pancreatectomy in rats. The food intake was kept constant. In one normal rat and in rats in which partial pancreatectomy caused no glycosuria, hypothalamic lesions caused hyperphagia which led to glycosuria. They found further that insulin sensitivity and glucose tolerance were not significantly altered in these obese rats. Bloch (256), on following the blood sugar levels after bilateral spherical lesions in the medial hypothalamus in cats, found little evidence of hypothalamic regulation. In contrast to these negative findings, Ingram (257) has greatly reduced or abolished the insulin requirements of totally depancreatized cats on a constant food intake, by placing bilateral lesions in the hypothalamus. A necessary requirement for a comparison of these results is detailed description of the lesions; those described by Brobeck *et al.* (255) are extensive and are not identical within their limited series.

Lesions in the hypothalamus depress for about three weeks the gaseous exchange of unanesthetized cats (258). It was not possible to correlate within the series of fourteen cats the various disturbances with the nuclear lesions, but in addition to the depression of respiratory metabolism, the lesions caused cachexia, or obesity, or in one case hemorrhagic erosion of the stomach.

The collection of data here reviewed makes painfully clear the need for systematic experiments in which metabolism, blood chemistry, and heat regulation are carefully studied after exactly localized lesions of the hypothalamus. Brobeck (259) has taken an important step in the right direction in arranging his rat cages where the activity, food intake, and room temperature may be varied independently. He is using this arrangement for systematic studies on his rats after hypothalamic lesions.

A clinical observation inviting experimental confirmation has been made on a boy with a localized autonomic epilepsy; while his symptoms were referable to the hypothalamus (260), the lesion

was in the thalamus (261). The dorsomedial nucleus was partly destroyed, and if it is the path through which the cortex is projected on to the hypothalamus, the "hypothalamic" attacks may be comparable to the seizures of sham rage seen after decortication.

*Cortical reflexes.*—Kennard (262) has found that the representation of the autonomies in the cortex is limited almost wholly to the frontal lobes, but that there is a different representation on each surface. If only one surface is removed, autonomic disturbances and changes in behavior occur; only total removal, which may be done in two stages, produces sham rage. Kennard considers the orbital surface of the frontal lobe as the cortical area of vagal representation, but the localization within one region of the cortex of functions as diverse as those influenced by the vagus seems improbable. Certainly vagal responses can be obtained from other cortical areas. Stimulation of the rostral cingular cortex (263) or the uncus (264) causes cardiac effects similar to those produced by direct stimulation of the vagus; and excision of the cingular cortex produced further evidence of its influence on vagal activity (265).

#### ANATOMY AND EMBRYOLOGY

Within the past few years, experimental embryologists have revealed the possibility of producing animals congenitally devoid of specific neural elements. It is not anticipated that the technique, which entails removing small parts of the embryo in early stages, will be applicable to mammalian forms, but if other vertebrate material of this nature is provided, a wholly new approach to the analysis of the autonomic nervous system will be opened. The first step toward this achievement is the identification of the rudiments of the various nerves, ganglia, and plexuses, but the localized removal of the proper embryonic tissue necessary for this identification is not easy. The use of stained embryos is helpful (266).

The origin of the sympathetic chain ganglia, attributed to the ventral part of the neural tube by Jones (267), has been reinvestigated by Yntema & Hammond (266) who have taken advantage of the spatial separation of the pre- and postganglionic neurons in the cervical region of the chick. The preganglionic neurons lie in the thoracic spinal cord and send their processes as far rostrally as the superior cervical ganglion; the postganglionic neurons lie along this trunk, considerably removed from the origin of the preganglionic fibers. When the occipital and cervical neural crests were re-



moved, without the possibility of damage to the thoracic neural tube, the cervical sympathetic ganglia failed to develop.

Another significant finding in these chicks was a deficiency of the neuroblasts of the enteric plexus after removal of the occipital crests. This is important since Jones (11), after removing the hind-brain from young embryos and finding a similar deficiency, concluded that sympathetic neuroblasts contributed nothing to the enteric plexus. The term "sympathetic neuroblast" connotes more than the experimental evidence justifies; the rudiments which contribute to the cervical sympathetic ganglia also contribute to the enteric neuroblasts (266). Perhaps it would be safer, and certainly more understandable, to refer to the rudiment rather than to the definitive form of the neuroblast.

There is no unanimity of opinion on the origin of the sensory ganglia of the cranial nerves. According to Yntema (268) "the branchiomic nerves possess sensory ganglia of two types in amniotes. The spinal type which arises from neural crest is the root ganglion. The epibranchial type is the trunk ganglion. In addition, there are motor components." Jones (11) shows a beautiful photomicrograph of the entoderm of the third pharyngeal pouch, apparently contributing to the formation of the nodose ganglion, but Yntema has experimental evidence, both in the chick (268) and in *Amblystoma* (269, 270) that the visceral sensory ganglia of the seventh, ninth, and tenth nerves arise from epibranchial placodes. The adherence of the placodes to the pharyngeal pouches does make it difficult to separate the contributions of each, but the removal of the placodes before their fusion, with a resultant absence of the ganglia, makes the entodermal contribution to the ganglia questionable.

Table I, modified from Yntema (268), summarizes the current information of the neurogenesis of the autonomic nervous system. Many of the interpretations are debatable, but the information on which they are based is too detailed for review (11, 266 to 270).

Anatomical analyses by Foley (271, 272) on the cervical sympathetic complex in the adult animal has changed the picture from the schematic to one of great factual detail. The sympathetic trunk of the cat contains a large number of vagal fibers, and both descending and ascending postganglionic fibers from aberrant ganglia (271). There is furthermore an amazing variation in the degree of myelination of the fibers (272).

While it has long been recognized that the splanchnic nerves contain sensory fibers, the demonstration that the majority are sensory is surprising (46). There are no vagal fibers in the splanchnics in dogs (273).

TABLE I

PROBABLE ORIGIN OF SOME AUTONOMIC NERVES AND GANGLIA IN THE CHICK

Definitive neural structure	Neurogenic rudiment			
	Neural crests	Dorso-lateral placodes	Epi-branchial placodes	Neural tube
VIII	Root ganglion	Lateral line ganglia	Geniculate ganglion	Preganglionic neurons
IX	Superior ganglion	Lateral line ganglia	Petrosal ganglion	Preganglionic neurons
X	Jugular ganglion	Lateral line ganglia	Nodose ganglion	Preganglionic neurons
Cervical	Root ganglia Sympathetic neuron (postganglionic)			
Thoraco-lumbar	Root ganglia Sympathetic neurons (postganglionic)			Preganglionic neurons
Sacral	Root ganglia Sympathetic (?) neurons (postganglionic) Enteric neurons (?)			Preganglionic neurons Enteric neurons (?)

The preganglionic visceral motor fibers of the facial nerve resemble those of the vagus and of the cervical sympathetic trunk insofar as myelination is concerned, and vary between two wide extremes. They constitute about 15 per cent of the facial nerve and leave it by two main branches, the greater superficial petrosal and the chorda tympani (274). According to Foley (275) most of the

fibers in the former are motor, while most of those in the latter are sensory.

The intramedullary course of vagal afferents has been followed by two techniques: Ingram & Dawkins (276) showed in Marchi preparations of the medulla after intracranial section of the nerve that the somatic afferents entered the trigeminospinal tract and that the visceral afferents went into the solitary tract. Harrison & Bruesch (277) recorded intramedullary potentials following stimulation of the cervical vagus; the area of electrical activity coincided with the respiratory region of Magoun.

Nonidez (278) has described and illustrated arteriovenous anastomoses in the sympathetic chain ganglia of the dog, but Bergmann (279) in a comprehensive study of the blood supply to the human celiac ganglion, saw none of these peculiar structures. Stöhr found multinucleated cells in the sympathetic ganglia from patients having asthma or Reynaud's disease (280). In dorsal root ganglia, Wein (281) found nerve endings about the sensory neurons. Their origin and significance is not at all clear, since they did not degenerate after transection of the dorsal roots or removal of the sympathetic trunks. The illustrations do demonstrate the feasibility of using photomicrographs for portraying nerve endings, even such complex ones as pericellular terminations.

The inferior mesenteric plexus has been analysed by Harris (282) through the use of fiber counts on nerves taken twenty-five to twenty-nine days after operations designed to eliminate selectively the different functional components of the nerves to the ganglia, a procedure which in itself presupposes an intimate knowledge of the plexus. Furthermore, the calculation involves the method of differences. The ratio of preganglionic fibers to postganglionic fibers was one to two. No ganglionic cell counts were made. It was estimated that there were twenty-five hundred afferent fibers proximal to the ganglion; five thousand distal to it. It would seem that the afferents divide in their passage through the inferior mesenteric ganglia.

The spleen of the rat and cat receives no vagal nerve supply demonstrable by anatomical techniques, but myelinated fibers degenerate after section of the splanchnics, while all fibers disappear after removal of the celiac and superior mesenteric ganglia (283). Studies of this type of the spleen, liver, kidney, and pancreas are long overdue.

Regenerating nerve is notorious for bridging gaps that are deliberately produced to deter regeneration, but Papez *et al.* (284) so effectively interrupted the splanchnic innervation of the adrenal medulla that no significant restoration occurred within two years. When less extensive excisions are made, the preganglionic fibers regenerate, sometimes establishing connections with postganglionic neurons of a different functional nature. When the cervicothoracic and the second thoracic ganglia are excised from the cat, the ascending preganglionic nerves regenerate up as far as the superior ganglion (285).

#### CONCLUSION

Perhaps the only reason that an antagonism between the craniosacral and the thoracolumbar divisions of the autonomic nervous system has been so energetically taught is that it provides the only basis for a simple functional classification of the nerves and ganglia. It now appears that this belief is false. It is perhaps fortunate that no other basis for cleavage of the autonomic system into various categories is satisfactory. The inadequacy of a classification into cholinergic and adrenergic systems has been cited before; it is applicable only to the postganglionic neurons. No morphological differentiation is apparent, and the information about the embryological origins of the different nerves and ganglia, which might provide the ideal understanding, is now in the rudimentary stages.

Perhaps it is more profitable to center attention on the similarities in structure and function and upon the central integration of the autonomic reflexes, rather than to exaggerate minor differences which can be demonstrated in the nervous control of different viscera.

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## THE SOMATIC FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM

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### INTRODUCTION

While the exigencies of the war have influenced the type of research, there has been a surprisingly large amount of fundamental investigation carried out and reported in the past year. True, most of these studies have been made in this country where the physical effects of the world conflict were not apparent, but from a number of the warring nations valuable papers have appeared on neurophysiological subjects having a direct bearing on military problems. It is impossible to discuss all aspects of somatic function in this review. Thus, the effects of anoxia on the somatic functions of the nervous system, the investigation of which has disclosed many interesting phenomena, will be presented in another section of the book. Certain other aspects of somatic nervous activity will be found in the chapters on Conduction and Synaptic Transmission in the Nervous System, Special Senses, Physiological Psychology, and Applied Physiology.

The outstanding contribution to the physiology of the somatic nervous system during the past year is the monograph on the precentral motor cortex edited by Paul C. Bucy (1) which was published in the fall of 1944 by the University of Illinois Press. Not only does it express the prevailing opinions of a group of well-known investigators in this field but it covers the pertinent world literature on the subject. The various contributions in this monograph will be referred to in detail under appropriate sections of this review.

### CEREBRAL CORTEX

The physiology of the cerebral mantle has been the subject of much investigation during the past year, particularly from the standpoint of its total function. The value of research upon the

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effects of conditions necessitated by combat techniques upon the human brain was early recognized. For this reason cerebral functions have been studied under conditions of hypoxia (see chapter on Aviation Medicine) and physical and mental fatigue (consult chapter on Applied Physiology), and during convalescence from somatic and nervous disorders. Some of these investigations have not yet been published in detail, but they give promise of elucidating many problems of cerebral function.

The general neuronal organization of the cerebral cortex has continued to be investigated. Using neuronographic techniques introduced by Dusser de Barenne, McCullough and his associates (2, 3) have elaborated their studies of interareal connections. The details of these relationships are too complicated to be given here; the interested reader should consult the original papers.

Experimental studies by Leão (4, 5) and Leão & Morison (6) indicate that moderate tetanic stimulation of the cerebral cortex of rabbits and cats results in a depression of electrical activity which slowly spreads over the cortex, passing off in five to ten minutes. This depression is associated with dilatation of the pial arteries, capillaries, and veins. It may spread to the hemisphere contralateral to the one stimulated, but such dispersion is dependent upon an intact corpus callosum. In the individual hemispheres, spread of the depression is independent of subcortical connections and of at least the three lower layers of the grey matter. Acute anemia of the cortex does not interfere with its propagation. These facts suggest that the process is not due to neuronal transmission of inhibitory impulses.

Forster & McCarter (7) have confirmed the findings of previous workers that acetylcholine applied to the cerebral cortex induces discharges which tend to remain sharply localized to the region of application. The occasional spread to an area of the opposite hemisphere was thought to be due to dromic spread along axones passing through the corpus callosum, for section of the latter abolished the secondary discharge. Rarely may a tertiary discharge be found, due to stimulation of the secondary neurone. The differences between the three types were to be found chiefly in the diminishing amplitude and degree of intervening cortical activity between discharges.

Davison & Demuth (8) call attention to a group of cases, clinically associated with pathological sleep, in which the patients on

postmortem examination were found to have lesions only of the cerebral cortex. The authors believe that some fibers concerned with the control of sleep originate in the cerebral cortex, especially the hippocampal, cingular, frontal, premotor, and temporal convolutions, and pass to the hypothalamus.

Numerous studies of the function of individual portions of the cerebral cortex have been reported in the past year. These will be discussed under a topical classification.

#### PREFRONTAL CORTEX

Although prefrontal lobotomy has continued to be practiced increasingly for the treatment of psychotic states, few reports in the past year have contributed to the knowledge of the function of this region of the brain. Ziegler & Osgood (9) report edema and trophic disturbances in the lower extremities as a complication of prefrontal lobotomy in eight of seventeen cases. The authors suggest that the vascular disturbance probably indicates that the prefrontal cortex is concerned in autonomic functions, although they admit that the lack of anatomic control makes it impossible to state definitely that complicating vascular lesions of the brain adjacent to the cuts might not have involved area 6 which is known to control vasomotor mechanisms.

The controversy over the effects of lesions of the prefrontal cortex on activity of the animal is revived by Mettler (10) in his discussion of the results of simultaneous bilateral frontal ablations. Mettler states that bilateral ablation of either area 8 or 12, or the posterior orbital gyrus (area 13) does not influence general bodily activity. Simultaneous removal of areas 8 to 12 causes a complex overactivity, whereas bilateral removal of area 9 or 6 produces an increase in a stereotyped ambulatory pattern. The latter syndrome is produced if areas 6 to 12 are removed with or without striatal damage.

#### PRECENTRAL MOTOR CORTEX

The electrically excitable frontal cortex has been the subject of the monograph previously mentioned. In it, von Bonin (11) presents the cytoarchitectural characteristics and areas of the precentral motor cortex in the light of recent physiological studies. The terminology used in the monograph is somewhat unusual. The area gigantopyramidalis is designated as area 4. Just in front of it

in the human brain is an area devoid of gigantic pyramidal cells in the fifth cortical layer which is area 4a (12). The suppressor strip rostral to area 4a is termed 4s. The inferior portion of the precentral cortex called 6b by the Vogt's becomes area 44. The upper portion of area 6 spoken of as 6a by the Vogt's is termed area 6 in accordance with Brodmann's terminology.

The thalamic projection to the precentral motor cortex (13) has been fairly well established for the higher primates, monkey and chimpanzee, although few data are available on the human thalamic projection. Area 4 receives a rich supply of fibers from the ventrolateral nucleus of the thalamus topically organized so that those entering the foot representation arise from the lateral portion, those to the face from the medial part, and the arm projection from the intermediate zone of the nucleus. The projection to area 6 becomes both absolutely and relatively greater as the primate scale is ascended. Area 4s appears to receive few, if any, fibers from the thalamus. Area 8 seems to receive its afferent supply from the nucleus medialis dorsalis of the thalamus rather than the ventrolateral nucleus.

The efferent fibers from the various areas of the precentral motor cortex in subhuman primates are more or less discretely arranged in the internal capsule and cerebral peduncle (14). With the exception of the corticospinal tract, the termination of these fibers in the basal ganglia, thalamus, brainstem, and spinal cord does not seem to be related to their areal origin. As the result of the anatomical examination of a human brain in which the premotor cortex (area 6) was removed for disabling tremor, Minckler *et al.* (12) state that area 6 sends fibers through the corpus callosum to the opposite area 6, to the superolateral aspect of the thalamus, and through the middle third of the basis pedunculis and medial portion of the pons with the corticospinal fibers to the anterior columns of the spinal cord.

The sequelae of extirpation of the precentral motor cortex in man are thoroughly discussed by Bucy (15), who presents a detailed account of most of the previous literature and of his own experiences. Removal of the arm or leg areas of the precentral motor cortex or both, in man results in a complete flaccid paralysis of the part or parts represented. The paralysis after removal of areas 4 and 6 begins to recede in four to sixteen days. The order of recovery is variable, but it progresses most rapidly in the proximal

muscles. Some of the distal muscles may remain paralyzed. The final deficiency is less severe when either the arm or leg area is removed than when both are ablated. In the upper extremity the flexor muscles, and in the lower extremity, the extensor muscles, show the greatest recovery. Spasticity appears within one or two weeks of the ablation. It is of the clasp-knife type and most marked in the stronger muscles, namely, the flexors of the arm and extensors of the leg. It is not so severe as that seen in hemiplegias due to capsular lesions. The tendon reflexes are immediately and persistently increased in the paretic extremities. Atrophy is present in the muscles involved by the precentral ablation. Marked alterations in sensation, touch, pain, pallesthesia, and stereognosis are observed in all cases to varying degrees but the author believes these alterations are due to secondary edema and vascular changes in the postcentral cortex.

In a discussion of the relationship of the precentral motor cortex to involuntary movements, Bucy (16) concludes that choreo-athetosis is mediated by fibers passing from the precentral motor cortex to subcortical centers and hence by fibers in the anterior funiculus of the spinal cord to the anterior horn cells. Intention tremor and tremor at rest are induced by fibers from the precentral motor cortex passing through the pyramidal tracts to the anterior horn cells. The possible circuits involved in the production of these movements are discussed.

*Area 4.*—The characteristic responses obtained by stimulation of the motor cortex have been known since the original paper of Bubnoff & Heidenhain which has been translated into English (17). The discrete movements particularly of the distal musculature following electrical excitation of the primate motor cortex including that of man have been recently reviewed (12, 18, 19).

As a corollary, extirpation of this area abolishes temporarily and impairs permanently fine digital movements (10, 20). Bilateral simultaneous ablation of area 4 produces a loss of adult ambulation and manual feeding patterns, so that the animal is unable to chew or suck immediately after operation (10). Mettler (10) states that such preparations show stiffness in all four extremities in the horizontal position, which he attributes to damage to area 4s. If a lesion of the postcentral gyrus is combined with one of area 4, the paresis is not only augmented but is spastic in nature (20).

*Area 4s.*—The results of stimulation of the suppressor strip

just anterior to area 4 in man are reported in one case (15, 21). Resistance to passive manipulation of the contralateral upper extremity was abolished by the excitation. Similarly, clonic afterdischarge induced by rather intense electrical stimulation of the arm motor cortex was arrested by excitation of the suppressor area.

*Area 6.*—Stimulation of this area in man is considered to induce complex synergistic movements of the contralateral extremities. In the chimpanzee, contraction of proximal muscles and simple synergistic movements of arm and leg result. In the macaque monkey, after section of the pyramids, stimulation with relatively low intensity currents induces movements of one arm and the contralateral leg and synergistic movements of the flexors and extensors (19). In man under avertin and ether anesthesia Mincker *et al.* (12) found that area 6 is inexcitable.

Removal of area 6 (including 4s) in the monkey is followed by a moderate spastic paresis (22). Although extirpation of areas 4 and 6 on both sides results in the usual clinical picture of spastic paralysis, bilateral simultaneous ablation of area 6 or areas 6 and 4s produces a paresis in flexion associated with reflex grasping (22) and increased resistance particularly in the flexor muscles on passive manipulation of the extremities. A coarse tremor aggravated by excitement develops in the affected extremities on voluntary movement. Welch & Kennard (23) state that this flexor pattern is an extrapyramidal release, but they give no explanation for the difference between this paraplegia in flexion and paraplegia in extension which is also considered a release from extrapyramidal control.

In keeping with the observation that certain stimulant drugs, doryl, strychnine, and thiamine, seem to have a beneficial effect on the rate and degree of recovery of motor function following ablation of areas 4 and 6 in the monkey, phenobarbital in doses having no observable sedative effect on cage performance produces marked slowing in rate of recovery (24). Dilantin does not seem to have this effect but if given with doryl the enhancing effect of the latter is not apparent.

*Frontal eye fields.*—In a detailed review Smith (25) presents the present knowledge of the cytoarchitecture, effects of stimulation and ablation of the frontal eye fields in experimental animals and man, without introducing new evidence or additional experimental findings.

*Cingular gyrus.*—Attention has been directed to the cortex on the medial surface of the frontal lobe in the past few years by the speculations of Papez (25a) that the cingular gyrus was concerned in emotion and the findings of Bailey *et al.* (25b) that a powerful suppressor area was located in that gyrus. By electrical excitation of that area in the monkey, Smith (26) found complex somatic and autonomic responses. The most striking response from the rostral cingular cortex was a vocalization characteristic of the animal. Sometimes this guttural cry was the sole response but frequently it was associated with a complex reaction including opening of the eyes, dilatation of the pupils, and facial movements. Even in the absence of vocalization, during which period respiration was altered, stimulation of the cingular cortex induced a decrease in rate or depth of respiration, or both, sometimes amounting to apnea for a few seconds. Usually during arrest of respiration the thorax was in a position of expiration, rarely inspiration. Permanent apnea could not be induced, the respiratory movements beginning spontaneously after a few seconds. Alterations in cardiovascular function were also seen, sometimes associated with vocalization. An increase in blood pressure of 20 to 30 mm. of mercury was seen after a latent interval of a few seconds. Following stimulation of the rostral cingular region bradycardia, associated with a fall in arterial pressure, was observed after a latent period of two to three seconds. A third type of cardiovascular response was a sudden arrest of cardiac action with a sharp fall in blood pressure, followed by a gradual return to normal or above normal. Section of both vagus nerves abolished the cardioinhibitory response.

Another striking phenomenon elicited by electrical excitation of the rostral cingular area was the cessation of spontaneous movements. Struggling was abolished, the animal's eyes closed, and it seemed to remain in a state resembling sleep for several minutes after the stimulation was stopped. In the absence of spontaneous movement, excitation decreased the resistance of the extremities to passive resistance, and stopped the afterdischarge following electrical stimulation of other cortical areas.

After a latent period of several seconds following stimulation of the rostral cingular gyrus the hair over the upper part of the trunk and upper extremities would slowly rise for a period of a few seconds. The piloerection was associated with a "gooseflesh" appearance of the skin.

## PARIETAL CORTEX

The functions of the sensory cerebral cortex have not received the attention in the past year that has been given to the motor areas. Although the cortical representation of the bodily segments has been determined for the subhuman primates, there are still gaps in our knowledge of the arrangement in man. Erickson (27) presents an unique case which has a bearing upon the cortical representation of the sacral segments. A fifty-two-year old woman suffered from nymphomania for twelve years before clinical manifestations indicated the presence of a brain tumor. Following the removal of a hemangioma between the medial surface of the brain and the falx near the longitudinal sinus, the patient had no further attacks and lost the abnormal sexual desire. As Erickson points out, the erotomania appears to have been the expression of cortical epileptiform discharge, which only occasionally spread to the more usual type of motor tonic-clonic discharge. The location of the tumor near the paracentral lobule suggests that the genitalia are represented in this area.

Further clinical evidence is presented for the cortical representation of taste in the parietal operculum rather than in the hippocampal gyrus. Shenkin & Lewey (28) report the case of a patient who suffered epileptic attacks initiated by an aura of sour or bitter taste without an olfactory concomitant. The perception of sweet was absent on the entire left side of the tongue, but present on the right side. The other tastes were appreciated equally on the two sides of the tongue. Olfaction was normal. At operation, an angioma was found over the lowest portion of the postcentral gyrus.

The parietal cortex of the cat according to Gobbel & Liles (29) has a fairly uniform six-layer cytoarchitectural structure with a somewhat wider molecular layer in the posterior part of the lobe. Betz cells are absent. From the parietal cortex association fibers pass into the posterior sigmoid and coronal gyri in large numbers. A few go to the anterior suprasylvian, fornicate, and rostral gyri. A moderate number of fibers enter the middle ectosylvian, lateral, and medial suprasylvian gyri. Some fibers pass to the splenius, lateralis posterior, and posterior suprasylvian gyri but none seems to go to the occipital lobe, anterior, middle, or posterior Sylvian gyri or to the extreme capsule. Commissural fibers pass through the corpus callosum to the contralateral lateral gyrus and some to the middle suprasylvian gyrus. Numerous projection fibers are present



in the internal capsule. Some enter the thalamus breaking up in the nuclei ventralis posterolateralis and pulvinar, although a few reach the nucleus ventralis posteromedialis, and posterior nucleus. Some fibers pass to the superior colliculus. Many go through the cerebral peduncles to reach the pyramids or pontine nuclei. The fibers from the parietal cortex in the pyramids cross and follow the lateral corticospinal tract to the cervical region of the spinal cord.

Peele (30) found in the monkey that electrical stimulation enabled a distinction between areas 5 and 7 and areas 3, 1, and 2. Flexion of the contralateral digits, or of the distal joints, or of both, was usually obtained from areas 3, 1, and 2 with 4 volts E.M.F. These movements resembled those obtained from area 4. Motor responses from areas 5 or 7 were obtained only with a greater strength of current. They usually consisted of elevation of the contralateral shoulder (sometimes both shoulders), protraction of the entire upper limb, or both. Contraction of the shoulder girdle was obtained by stimulation of the anterior part of area 7 and inferior part of area 5 lying along the anterior lip of the intraparietal sulcus.

Removal of area 3, areas 1 and 2, area 5 and area 7 individually or of areas 1, 2, 5, and 7 in combination from the parietal lobe of a monkey resulted in a disinclination of the animal to use the contralateral extremities but no real paralysis (30). Ablation of area 3 or areas 1 and 2 affected the contralateral arm and leg equally; removal of area 5 affected the leg and area 7, the arm particularly. Hypotonia, pronounced in the proximal muscles, was found in the affected limbs for as long as a year after operation. Probably due to the hypotonia, the affected limbs appeared slow in movement and ataxic unless the animal watched the movement of the limb. The tendon reflexes were more difficult to obtain and more pendular in character. Tactile and noxious stimuli were not reacted to initially nor for many months if the postcentral gyrus was involved. Localization of the stimuli was severely impaired. The placing and hopping responses to proprioceptive and tactile stimuli were absent initially. Tactile placing never returned to normal after postcentral lesions.

In spite of the wealth of material afforded by the global conflict, very little has been written during the past year of the effects of wounds of the parietal cortex in man. That many important observations have been accumulating seems likely, and in the next few years the results of these researches should be apparent.

Bender (31) has examined a series of patients suffering from wounds of the brain, spinal cord, or peripheral nerves, in which cutaneous sensory disturbances were present. He found a dulling of cutaneous sensation in an area with deficient innervation when corresponding points on the two sides of the body were simultaneously stimulated. The most easily dulled sensory modality was graphesthesia, the least vulnerable, pallesthesia. The appreciation of pain in the affected area when bilateral stimuli were simultaneously applied showed a reduction in adaptation time, with a rise in threshold, or total extinction of the perception. When only the affected area was stimulated the appreciation of the particular modality was usually normal or only slightly impaired. Bender believes that the phenomenon is due to thalamic or cortical mechanisms.

#### OCCIPITAL CORTEX

On the basis of animal experimentation, the arrangement of the geniculocalcarine projection is well established. That it is precisely the same for man has not yet been conclusively demonstrated. For this reason injuries of the striate area in man still have physiological and anatomical interest. Bender & Furlow (32) present a case of bilateral occipital lobe damage. Following a period of complete amaurosis, vision in the peripheral fields returned with gradual diminution of the central scotomata. Movement was best perceived, color slightly, and form poorly. The vision was better under low illumination so that night vision was better than day. In spite of central scotomata objects were perceived as a whole. The psychological fixation point was retained and the patient did not recognize that he had central scotomata even when they were demonstrated to him. Later when a new functional fovea developed, he was convinced of his blind anatomical fovea.

Modification of the spontaneous electrical activity of the cerebral cortex of cat, dog, monkey, and man may be produced by intermittent photic stimulation of the retina, so that the electroencephalogram obtained from the occipital cortex may take on a frequency synchronous with that of the flicker (33). The effect is augmented by increasing the intensity of the luminous flux with a maximum at approximately 80 foot candles. The driving is more pronounced when the photic stimulus is at the blue end of the spectrum than when it is at the red end. The cortex of the macaque

monkey may be made to follow a flicker with a frequency of 34 per second, but the optic nerve and the lateral geniculate body will follow frequencies of 62 and 59 cycles per second respectively. Lesions of the visual pathways impair photic driving (34).

Investigations of visual functions during the past year have largely concerned the more complex phenomena associated with vision. Developing further the concept of the dynamic visual field Halstead (35, 36) has shown that if two objects be presented simultaneously tachischoscopically one at the fixation point and one at the periphery of the visual field, both are perceived by the normal individual. Under certain circumstances with full peripheral fields to perimetric and Bjerrum screen examination, the seeing field for such simultaneous presentations may be markedly constricted. This constriction of the dynamic visual field is found in frontal lobe lesions, posttraumatic cerebral syndromes, and following cerebral anoxia.

Somewhat akin to this phenomenon is visual extinction. Bender & Furlow (37) found in a patient recovering from a gunshot wound of the left occipitoparietal cortex, that visual stimuli presented in the normal homonymous field of vision tended to suppress or dull an image originating simultaneously in the opposite affected field of vision. The greater the stimulation in the normal field, the less the patient saw in the other field. This visual extinction was considered associated with the psychological factors of rivalry, dominance, and attention mechanisms.

Another peculiar associate of visual disturbances is the denial of blindness by patients suffering from cerebral disease. Redlich & Dorsey (38) discuss the literature and present six cases. Two were due to retinal lesions and the remainder to cerebral involvement of the visual pathways. All showed mental impairment such as disorientation, severe impairment of recent memory and retention, and confabulation. The authors suggest that the interference with corticothalamic circuits is responsible for the syndrome.

#### TEMPORAL CORTEX

Studies of the function of the temporal cortex during the past year have been confined to the auditory representation. Tunturi (39, 40) has examined the localization in the dog of cortical responses to auditory stimuli. Three areas in the cerebral cortex have been found. A dorsal area lay in the middle ectosylvian gyrus. In

this zone high frequencies were located anteriorly, low frequencies posteriorly, and successive octaves were arranged at equal intervals along the cortex. The ventral area had a higher threshold and the frequencies were inversely arranged. From the anterior ectosylvian gyrus responses were obtained to audio frequencies of 100 to 400, from the posterior gyrus responses to frequencies of 8000 to 16,000, and over the sylvian gyrus and middle ectosylvian sulcus, responses to intermediate frequencies were found. A third area (10 to 20 mm. square) was found at the junction of the anterior ectosylvian gyrus and the coronal gyrus (the anterior composite gyrus). Each ear was represented bilaterally but somewhat more strongly on the contralateral side. Electrical stimulation of the bony spiral of the cochlea with cortical recording confirmed the localization demonstrated by auditory stimulation.

Removal of any one of the three areas or the second and third areas bilaterally caused little or no delay in the appearance of previously acquired correct conditioned differential responses of the foreleg to auditory stimuli (41). Ablation of the first two cortical zones disrupted conditional reflexes which could be reacquired. If all three areas were removed, Allen (41) found that the correct conditioned differential response was abolished for at least six months.

#### SENSATION

*Pain.*—Investigation of the sensory functions of the nervous system has not been emphasized in the past year. However, a number of interesting observations have been reported. The frequency of peripheral nerve injuries and the occurrence of pain during regeneration have been noted in military casualties (42). In general, the pain is most severe in partial injuries of the median or tibial nerves (or the tibial component of the sciatic nerve). Causalgic pain is characterized by a peculiar burning quality unrelieved by medical means other than the use of opiates. Some amelioration may be obtained by the application of cold or occasionally warm packs to the hand or foot. The slightest irritation of the member causes an exacerbation of the pain so that the patient desires to be alone. Even noises or light may set up a paroxysm. In the less severe cases and later in the more severe cases, the pain may be described as a crushing, boring, or a gripping pain which at times has a burning quality. It prevents use of the

member which soon develops fibrosis and contractures about the joints. The affected extremity may have a cold atrophic glistening hyperhidrotic skin with loss of hair and curling nails on tapering fingers. In this type of extremity oscillometry usually shows a vasoconstriction and skin temperatures are 2 to 6° F. lower than those of the normal limb. In the majority of cases, however, the skin is dry, scaly, and warm with long coarse hair. The skin shows vasodilatation and has an elevated temperature (43). Such cases usually obtain relief from cold water and are made worse by heat. Practically all cases show a hypersensitivity to sympathetic stimulation as evidenced by the aggravation of the pain by sudden noise and emotional upsets.

Although the condition may be associated with evidence of psychological instability (44), the incidence of psychoneurotic personalities in patients suffering from the condition is no higher than that in a similar group taken at random from the general population. Since the condition may be relieved by sympathectomy in practically all cases, an overactivity of the sympathetic nervous system has been postulated. The mechanism of this hyperactivity has not been explained. Porter & Taylor (45) have suggested that the phenomena may be reduced physiologically to facilitation of the impulses from the damaged nerve by cutaneous stimuli. They showed that the flexion reflex was augmented by cutaneous or other forms of stimulation of the foot simultaneous with rhythmic faradic excitation of the cut sensory nerve. Causalgia, they suggest, is due to cutaneous stimuli facilitating impulses from the site of injury. Granit *et al.* (46) showed that cross stimulation between motor and sensory fibers may occur at the site of injury. By means of the cathode ray oscillograph they demonstrated an afferent discharge of the sensory root when the motor root was stimulated. They believe that the poorly- or nonmyelinated C fibers are especially susceptible to this "fibre-interaction." Doupe *et al.* (47) suggest that efferent sympathetic fibers may be the cause of the stimulation of the afferent sensory fibers.

Bender (31) calls attention to the fact that in causalgia, stimulation of the area on the opposite side of the body corresponding to the site of pain accentuates or precipitates a paroxysm of pain. At times the causalgia spreads to the opposite side. Bender suggests that these phenomena may be due to pain fibers transmitted by the vascular tree. Another explanation of this is suggested by

the observations of Ray & Wolff (48) on the spread of pain. They found that noxious stimuli applied to an extremity partially denervated (analgesic and thermoanesthetic) as the result of a contralateral chordotomy evoked a rather diffuse pain referred to the other side of the body at a point corresponding to the site stimulated. Irritation of the normal side did not cause pain on the abnormal side. Ray & Wolff conclude that pain fibers have inter- and intrasegmental relationships. These connections may be the anatomic basis for the facilitation phenomena mentioned by Bender.

The causes of facial pain are numerous, and relief is not always easy to obtain (49). Trigeminal neuralgia is a well known clinical entity, although its pathological basis has remained a mystery. An interesting mechanism for this type of pain is proposed by Karl, Peabody & Wolff (50). They found that vasodilator drugs such as histamine, amyl nitrite, carbon dioxide, or nicotinic acid diminished or eliminated the pain and rendered "trigger areas" no longer excitable. The longest lasting effects were obtained with nicotinic acid and amyl nitrite. Repeated daily administration markedly relieved all patients. They suggest that the pain is due to reflex vasoconstriction evoked by afferent stimuli from the trigger points.

Although surgical methods for the relief of pain have been discussed (51), no new techniques have been presented in the past year.

*Other somatic sensations.*—No significant advances in the knowledge of somatic sensory function have been reported in the past year. One interesting phenomenon associated presumably with a softening of the thalamus has been reported by Halpern (52). As the sense of position and stereognosis in the hand returned to normal, objects placed in the affected hand seemed more bulky and massive than when placed in the normal hand. Thus the same key placed successively in the hands was recognized as a key, but the patient insisted he had been given two keys, a larger one in the affected hand and a smaller one in the normal hand. Upon visual inspection of the objects felt, he stated that the object in his affected hand was smaller than he had imagined. This abnormal perception involved the entire side of the body, abruptly stopping at the midline, so that an object crossing the midline felt irregular and bulkier on the affected side. This macrostereognosis is analogous to macropsia in the visual sphere.

*Vestibular function.*—The role of vestibular function in the

maintenance of normal cerebral activity has been emphasized by Spiegel *et al.* (53). In the cat the cerebral circulation, as determined by intracerebral thermocouples, was found to be slowed by labyrinthine stimulation. This reaction is due to a fall in systemic blood pressure, since interruption of the cervical sympathetic nerve and the vasodilator tract joining the facial and great superficial petrosal nerves does not abolish the responses. This phenomenon may be a factor in the Bruns syndrome (54), which is composed of three features, (a) the development of attacks of vertigo, headache, and vomiting on change of posture of the head, (b) a freedom from symptoms between the attacks, and (c) a constant anterior flexion of the head with or without lateral flexion or rotation. Since this syndrome is frequently due to a tumor of the fourth ventricle, a hyperirritability of the vestibular and perhaps also of the glossopharyngeal centers subserving the carotid sinus mechanisms may play a more important role in the syndrome than the purely mechanical factors which previously have been considered responsible.

*Audition.*—The peripheral auditory mechanisms are discussed in another section of this book. One observation is noteworthy here since it concerns other somatic functions of the nervous system. Wells (55) has reported that monoaural stimulation results in augmentation of contralateral and inhibition of ipsilateral extensor tone of the arm or leg of man. Flexor tonus, as would be expected, is conversely influenced.

#### BASAL GANGLIA

From the laboratory of F. Bremer of Brussels, Gerebtzoff (56) reports on the effect of stimulation of the striate bodies of the rabbit. He found that simultaneous stimulation of an area of cortex inducing mastication and any of the nuclei of the striatum caused an inhibition of the cortical response. Depending upon the strength of the striatal stimulation the cortical response was partially or totally abolished. The inhibitory effect which lasted thirty to forty-five seconds after striatal stimulation influenced only movements induced by excitation of the homolateral cortex. No evidence of somatotopic localization was found in the striatum. Stimulation of the pallidum did not inhibit cortically induced mastication, but caused a depression of the lower jaw which persisted for about one minute after the stimulation. There was no evidence of localization within the pallidum. The author concluded that the effect of the striatum is inhibitory upon the cerebral cortex.



Combined frontal and striatal lesions, even if unilateral, in the primate may produce an impulsion to climb and a hyperkinesia (57). If the pallida are significantly injured, a bradykinesia and tendency to retain abnormal postures develops. This striatal pattern was seen by Richter & Klüver (58) in a monkey suffering from spontaneous bilateral striatal degeneration involving the putamen and globus pallidum. All forms of spontaneous activity were depressed, and there was no evidence of chorea.

As clinical confirmation of the experimental production of chorea, Chang (59) described a dog which had choreiform movements confined to the left hind leg, and involuntary nodding of the head. Histologically the lesions were focal encephalitic areas in both putamens and in the deeper cortical layers of the medial part of the right posterior sigmoid gyrus.

Morison & Bassett (60) found that bursts of spikes eight to twelve per second, such as are seen in normal relaxed cats were recorded from the thalamus and basal ganglia as long as three days after decortication, section of both optic nerves, and midbrain severance. It is assumed that the cortex is not essential for such activity.

#### CEREBELLUM

Experimental studies of cerebellar function have been singularly few in the past year. Bailey (61) reviews the recent literature on cerebellar function in his discussion of the relationship of the precentral motor cortex to the cerebellum. An intriguing and unique study of cerebellar function is presented by Snider & Stowell (62). In cats the application of appropriate tactile, auditory, and visual stimuli evoke discrete potential changes in definite areas of the cerebellar cortex. The receptive areas for tactile stimuli are located in three parts of the cerebellum. In each lateral half of the anterior lobe and adjacent folia there is a topical representation of the ipsilateral half of the body surface. The feet are represented bilaterally, the forefoot having a stronger contralateral projection than the hind foot. The auditory area is largely confined to the lobulus simplex and the tuber vermis. The responses are abolished by section of the auditory nerves, destruction of the cochlea, or ablation of the inferior colliculus. The visual area overlaps the auditory and in most cats the two areas are conterminous. Sodium pentobarbital anesthesia has little effect on the cerebellar responses to tactile stimuli but markedly depresses the auditory potentials and abolishes the visual responses.

## BRAINSTEM

The functions of the brainstem and its component parts, in particular the long tracts passing through it, continue to be elucidated by both old and new techniques.

*Effects of sectioning the cerebral peduncles.*—In view of the present interest in the genesis of spasticity, the observations of Cannon *et al.* (63) on a series of six monkeys after section of the basis pedunculi are quite pertinent. The animals had a severe paresis of the contralateral extremities associated with hypotonicity of all muscle groups except the extensors of the digits, but hyperactive tendon reflexes without clonus. The authors suggest that the inhibitory pathways originating in the cerebral cortex, which, interrupted, give rise to hypertonicity and clonus, must deviate from the corticospinal tracts before the latter reach the cerebral peduncles.

*Decerebration.*—Although it is generally considered that transection of the brainstem between the upper medulla and the cephalic portion of the midbrain induces an extensor rigidity, Keller (64) found in the dog an enduring generalized muscular atonia when the transection was appropriately placed in the cephalic part of the pons. After recovery from the anesthetic the animal was limp and no resistance to passive manipulation was encountered in any of the striated musculature. The positive supporting reflex was absent. The knee jerks were brisk and occasionally the response radiated to the other side. The crossed extensor and scratch reflexes were absent. The flexion reflex was absent for a few days but gradually became stronger. By careful nursing some of these animals were kept alive for four weeks.

When the transection passed through the middle level of the midbrain (middle of the anterior corpora quadrigemina and exit of oculomotor nerves) the righting reflexes were immediately absent but gradually returned. After a few days the animal could stand and walk. There was never hypotonus and only infrequently extensor rigidity.

When the transection passed through the caudal part of the midbrain, the muscle tonus was normal or reduced. Usually the atonic animals developed a normal tone. Righting reflexes were impaired but the animal could stand after a time.

Transection through the middle or caudal part of the pons immediately induced in the dog an absence of all righting reflexes although the muscles exhibited normal tone or extensor hyper-

tonus. Keller emphasizes that these varying effects are not due to accidental damage to the hindbrain.

*Periaqueductal grey substance.*—In the cat a lesion of the periaqueductal grey matter produces a state of profound "suspension of animation." Bailey & Davis (65) have repeated the experiments in monkeys. While the reactions varied somewhat, all showed a marked inactivity without other evidence of neurological abnormality. This reduction in drive rapidly developed to practically complete indifference to any external stimulus except food. When aroused, the animals reacted but gradually relapsed into an indifferent state. The animals lived from nine to thirty-five days following the lesion. The cause of death was not evident, for no lesion except that in the midbrain was found.

*Medullary control of vasomotor regulation.*—The influence of the medullary structures on vasomotor regulation and particularly capillary permeability is emphasized by a case reported by Schlesinger (66). A healthy boy was struck by a chisel, a fragment of which penetrated the lateral aspect of his medulla oblongata. The patient was only momentarily dazed but over a period of twelve hours developed a severe pulmonary edema to which he succumbed within twenty-four hours.

*Auditory pathways.*—The pathways of the auditory tracts in the brainstem have been fairly precisely determined. In view of discrepancies between anatomical and physiological accounts of auditory function, Ades (67) reviews the midbrain auditory mechanism in cats. Primary neurones from the spiral ganglion of Corti send their axones to terminate in the cochlea nuclei. Secondary neurones may cross to the lateral lemniscus to end in the inferior colliculus, or they may terminate in either the homo- or contralateral superior olivary nucleus. From this nucleus tertiary fibers ascend in the lateral lemniscus of the same side to end in the posterior corpus quadrigeminum or the medial geniculate body. Other tertiary neurones in the posterior corpus quadrigeminum send their axones by way of the brachium of the posterior corpus quadrigeminum to the medial geniculate body or across the midline to end in the opposite posterior corpus quadrigeminum or in the opposite medial geniculate body. Some axones of third order neurones reach the anterior corpus quadrigeminum. The contribution of the contralateral ear to the collicular response is slightly greater than that of the homolateral ear. A significant number of fibers bypass the posterior corpus quadrigeminum passing directly to the medial

geniculate body. The posterior corpus quadrigeminum however, appears to be capable of auditory integration.

*Optic projection on the anterior corpus quadrigeminum.*—Although it has been known for years that fibers of the optic tract pass to the anterior corpus quadrigeminum and that electrical potentials from that mass are altered by photic stimulation, the details of the projection have not been determined. Using an electrophysiological method, Apter (68) has mapped out the retinal projection on the anterior corpus quadrigeminum of the cat. The temporal retina of the left eye and the nasal half of the area centralis of the right eye are projected only upon the left anterior corpus quadrigeminum. The lower part of the retina is represented medial to the upper part of the retina on the anterior corpus quadrigeminum. Points along the vertical meridian are projected at the anterior end of the anterior corpus quadrigeminum. Points 110° temporal to the vertical meridian of the visual field of the left eye are represented at the posterior end of the right anterior corpus quadrigeminum.

*Medial longitudinal fasciculus.*—The medial longitudinal fasciculus consists mainly of fibers arising from vestibular nuclei. Stimulation of this tract in monkeys causes ocular adduction (69). Destruction of the tract results in paralysis of adduction of the eyes and nystagmus in the abducted eye upon attempted lateral gaze. Vestibular function remains intact. The medial longitudinal fasciculus probably represents the terminal part of the corticobulbar pathway for horizontal movements of the eyes.

*Pyramidal system.*—The pyramidal tract in monkeys and man (70, 71) has continued to be the subject of considerable investigation. It is evident that the pyramidal tract contains fibers originating not only from area 4 but from all areas of the parietal cortex (30). Perhaps in the human, Tower (72) states, the pyramidal tract may have an even more extensive origin. That all the fibers have a cortical origin is not definitely proven, although Welch & Kennard (22) state that hemidecortication in the monkey is followed by total disappearance of all fibers demonstrated by the Weigert technique. Since many of the fibers are unmyelinated (39 per cent), evidence based upon a myelin stain cannot be considered adequate proof.

The pyramidal tract in cats, monkeys, and chimpanzee (70) is responsible for the somatotopically organized control of discrete movement, for its section abolishes such responses. Pyramidal le-

sion in the cat and monkey produces a hypotonic paresis according to Tower, but Lidell & Phillips (73) suggest that the hypotonicity may be due to fillet damage. In their experiments on the cat they found that if the animal were placed with its rump on the observer's lap, the hind limb on the affected side was more extended than the leg on the other side. This extensor tonicity which lacked a "clasp-knife" character was even more evident upon eliciting the magnet reaction. It persisted two to six weeks, gradually subsiding. The paresis following pyramid section (72) affects fine movements in particular, so that precise skilled performances are severely impaired. The placing and hopping reflexes are defective (72, 73). The affected side is conspicuously colder than the opposite side. In man, no uncomplicated case of pyramidal lesion has been reported, but Tower (72) describes probably the best example of a nearly pure incomplete lesion. The patient, still alive, has a flail-like paresis of the limbs with a loss of fine movements of the involved extremities. The reflexes are increased, the muscles atrophic but without contractures. There is tonic innervation of the hand-grip requiring the use of the normal hand to open the fingers. The plantar reflex on the affected side is extensor with fanning of the toes. The skin temperatures on the affected side, especially in the extremities, are lower than on the normal side. Tower points out that results of pyramidal section are not in accord with the clinical concept of pyramidal lesions in man, as a "spastic paralysis." This syndrome is the result of pyramidal and extrapyramidal involvement. She considers the most reliable sign of a pyramidal lesion the loss of discrete control of movement. True, the Babinski sign in man appears to be evidence of pyramidal involvement, but Lassek (71) reaffirms that this sign may be elicited in persons with no loss of pyramidal tract fibers, and under certain conditions in individuals without other evidence of neurological disease.

#### THE REACTIONS OF THE BRAIN TO TRAUMA

During the past few years, stimulated by its obvious importance for military medicine, considerable research has been carried out on the reaction of the brain to trauma. This work has centered about four phases of the problem, (a) physical factors involved, (b) neuronal reactions, (c) vascular reactions, and (d) anatomical alterations. While the investigations have clarified the issues in-

volved, they do not seem to have settled the question as to the fundamental nature of cerebral concussion.

*Physical factors.*—Denny-Brown & Russell (74) called attention to the fact that cerebral concussion may be due to a crushing injury of the skull or to a blow causing a sudden rapid deceleration or acceleration of the head. They believed that these two types of injury were distinct clinically and physiologically. In the crushing injury the concussive phenomena were the result of a compression of the intracranial contents, and they referred to this type as compression concussion. Blows causing acceleration or deceleration of the head, they believed caused no significant increase in intracranial pressure. The cerebral concussion so induced was considered a generalized reversible molecular neuronal reaction, the result of the high rate of change of velocity.

This concept of compression and acceleration concussion has been challenged by workers (75, 76) who could find no clinical difference between the cerebral concussion induced by striking a fixed as opposed to a moveable head. Moreover, the basis of the physical differentiation was questioned when more accurate methods of measuring intracranial pressures were used (77, 78). For it was then found that in acceleration concussion the intracranial pressure was raised momentarily as high or higher than in compression concussion. In a recent paper Denny-Brown (79, p. 314) admits that "the rapid physical phase is a condensation of the whole brain, that is compression." He states that this physical condensation of nervous tissue is the basis of concussion. Other investigators (80) stress that not only rapid condensation but rapid expansion of the cerebral tissues occurs when the head is struck and would favor the idea that it is this shaking up of the nervous tissue which produces concussion.

Two factors have been shown to play a role in the rapid changes in intracranial pressure at the moment of a concussive blow. One is the vibration of the calvaria, and the second the pressure wave transmitted through the brain. The speed of propagation of these waves differ, that of the calvaria being considerably faster than that passing through the brain so that ample opportunity is afforded for secondary waves to be produced which may cause shearing strains. The rapid propagation of the vibration of the skull with resultant fracture may be the explanation of lack of cerebral concussion in many cases of skull fracture. The fracture serving as a

decompression causes the pressure wave propagated through the brain to be damped rather than reflected, hence shearing strains, which are particularly apt to cause neuronal injury, are less likely (81 to 85).

*Neuronal reactions.*—The old theories that cerebral concussion is due to cerebral anemia have been discarded, particularly since it has been shown that the brain is not anoxic at the time of or following concussion (81, 86). Most authors now conclude that neuronal reactions are at the basis of the concussion but there is no unanimity of opinion as to the nature of these reactions. On the basis of an analysis of the clinical and electroencephalographic alterations during cerebral concussion, Walker *et al.* (80) have suggested that the mechanism of simple concussion is a traumatic excitation of many cells of the brain. In some animals cerebral concussion is characterized by initial convulsive manifestations, in others, by what appears to be an initial depression of cerebral function. Walker *et al.* (80) state that at the moment of concussion they were able with suitable recording apparatus to demonstrate a potential discharge in the brain followed by increased electroencephalographic activity for two to twenty seconds. Dow *et al.* (87) using a hammer as a striking object have not been able to confirm this finding. But a hammer causes such a large potential artefact that small biological discharges might be masked. Moreover, the fact that Dow *et al.* (87) did not find evidence of increased cortical activity in their dogs immediately after the blow might be due to the fact that their amplifiers were blocked for from three to five seconds after the blow. Williams & Denny-Brown (88) found an immediate decrease in cortical activity but their animals were under pentobarbital anesthesia which Walker *et al.* (79) maintain inhibits the afterdischarge following cortical stimulation. Dow *et al.* (87) conclude as did Denny-Brown & Russell (74) that concussion has a direct paralyzing effect, temporary in nature, independent and beyond the mechanical stimulation of neurones.

Although the exact neuronal process is not agreed upon, most workers concur that certain nerve cells are more severely affected in cerebral concussion than others. The primary motor and sensory systems are less depressed by the injury than the secondary systems and internuncial cells. Thus Groat *et al.* (89) found that the electrical excitability of the motor cranial nerve nuclei are little altered in concussion, whereas the irritability of the supranuclear centers, brainstem, tegmentum, hypothalamic, and cerebral cor-



tex are markedly depressed. In the sensory sphere photic driving is actually augmented by concussion, although the general activity of the cerebral cortex is diminished (75). Electroencephalographic evidence also points to a specific effect upon certain neurones (81). Denny-Brown (79, p. 309) concludes that cerebral concussion "is characterized by excitation followed by a refractory interval which varies from neurone to neurone, being most brief in the respiratory center and most prolonged in some portions of the cortical apparatus."

*Vascular changes.*—Following cerebral concussion it has been shown that vasomotor changes occur which probably influence the permeability of the cerebral capillaries allowing cerebral edema to develop within a few hours (90) and impairing the vasomotor control of the cerebral vessels (81). The metabolism of the brain as reflected by its chemistry does not appear to be significantly disturbed by cerebral concussion.

*Anatomical alterations.*—Windle *et al.* (91, 92) have emphasized that cerebral concussion in the experimental animal is accompanied by subtle changes in the cells of many nuclei of the brain stem, in particular the internuncial neurones. The cells of the vestibular nuclei are always affected as well as scattered large cells of the tegmentum of the midbrain, pons, and reticular formation on either side of the median raphe. With increasingly severe blows, cells of the red nucleus, nuclei of the trigeminal tract, medial vestibular, and cochlear nuclear become involved. Primary motor neurones are not damaged.

These findings correlate with the observations that suprasegmental structures are more affected by cerebral concussion than cranial nerve nuclei (89).

These investigations have given a new impetus to the study of cerebral trauma. From the mass of accumulating and as yet somewhat confusing data, the real solution to the problem of cerebral concussion may be attained. It is good, though, that the experimental evidence is being critically analyzed.

#### THE EFFECT OF AGE UPON THE SOMATIC FUNCTIONS OF THE NORMAL AND ABNORMAL CEREBRAL CORTEX

It has been known from the work of Hines (19) that the maturation of the precentral gyrus of the macaque monkey, in terms of responses to electrical stimulation, proceeded in an orderly fashion. True, the observed spontaneous movement of the animal did not

necessarily correspond to the movements elicited by electrical stimulation. Progressive movements and isolated digital movements were not observed in the fetus removed by Caesarian section, although both were present on cortical stimulation. Later, from one month to a year, the increasingly more complex spontaneous movements and those obtained by electrical stimulation of the cerebral cortex showed close correspondence, although differences were still apparent.

Kennard (93) has analyzed the motor patterns after various lesions of the cerebral cortex. Whereas the adult decorticated monkey has a very limited motor performance, the decorticated infant has a more complex pattern. It exhibits righting reflexes, stands, and walks. Its posture is an exaggerated flexion without spasticity. Although many parts of the cerebral cortex have a capacity for reintegration of function lost by ablation of an area, the occipital lobes do not appear to have such propensities, nor do the other cortical areas for the visual functions.

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## AUDITION

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As a result of the war, activity in the auditory field continues to be devoted mainly to auditory testing, pathological states, and the rehabilitation of the deafened. Research on the more fundamental problems of hearing has dwindled almost to the vanishing point.

*Audiometry.*—A need which is emphasized in war-time is the rapid testing of auditory acuity in large numbers of persons. Two improvements over the ordinary individual tests have been developed. One is an abbreviated test that rapidly screens out the larger number of normal ears, and leaves the doubtful ones for more rigorous examination (1). Another that is suitable for adults who can keep their own scores is a group test (2). The group methods have not served well for children (3). When no sound-proof room is available, and there is a considerable background of noise, enclosures over the ears are a help, provided that they are fairly large, and so do not produce an effective closure of the ears and thereby alter the bone-conduction threshold (4).

The detection of auditory malingering is a difficult matter, and the routine audiometric procedures are inadequate. Generally the malingerer pretends to be deaf in one ear, and a number of tests seek to distinguish this simulated deafness from true unilateral impairment. Priest (5) has described several methods, of which the best is Stenger's test or a form of it, which is based upon the principle that if the two ears are stimulated unequally by the same sound the listener hears one sound only and refers it to the more strongly stimulated ear. Hence the malingerer will deny all hearing when the supposedly deaf ear is the more strongly stimulated even though the "good" ear is being excited at a level well above its threshold, and so he is exposed. While ordinarily used with tuning forks, this test can be carried out conveniently with an audiometer provided with certain simple accessories (6).

The computation of a single measure of auditory impairment as a percentage loss, on the basis of threshold measurements at discrete frequencies, has had continuing attention, most often with

a note of criticism, yet Utley (7) finds high correlations between speech discrimination ability and all of five methods of computation that have been proposed.

*Deafness.*—The assessment of war damage to the ears must be made on the basis of control studies of officers and enlisted men prior to combat. Such a study for aviators is reported by Senturia (8). One of the causes of ear damage is over-stimulation by sounds. In many instances there is partial recovery, which evidently continues over a period of time but is maximal in about two months (9). As animal studies have shown, the more extreme stimulations damage the organ of Corti and little repair is possible (10). On the other hand, blast injury usually involves the conductive mechanism as well as the inner ear. Susceptibility varies enormously among individuals, but most persons exposed to heavy gun blasts over long periods suffer at least moderate impairments, especially to the tones of 2896, 4096, and 5792 cycles (11). The behavior of the conductive mechanism during exposure to blast has been observed by Perlman in fresh cadavers by attaching minute mirrors to the moving parts (12, 13). A new theory of drum rupture due to blast is offered by Cantor (14); in opposition to the usual notion that the negative pressure wave is responsible, he suggests that usually during the positive wave a pressure is built up in body cavities which then ruptures the drum outwards.

Flying presents particular hazards to the ears. Descent from high altitudes, with consequent positive pressure on the drum, causes inflammatory changes resembling acute infectious otitis media, with loss of hearing usually to high tones but often to low tones as well (15, 16, 17). The effects are most serious in persons whose auditory tubes do not open properly to ventilate the middle ear (18). This condition is frequently due to hyperplasia of lymphoid tissue near the orifices of these tubes, and careful examinations, with tests to show the effects of pressure, will disclose the persons especially liable (18, 19). The wearing of ear plugs to guard against sound trauma complicates the problem of pressure equalization by closing off the external meatus (20).

Guild (21) has made a thorough-going study of histological otosclerosis, in an examination of serial sections of the temporal bones of 1161 patients. Of this number forty-nine showed otosclerotic areas in one or both ears, for a total of eighty-one ears; yet out of this eighty-one only ten showed ankylosis of the footplate of the

stapes and consequent auditory impairment, or clinical otosclerosis. In most of the ears without clinical indications the otosclerotic areas were within 0.2 mm. of the stapes, and it is unexplained, and possibly only accidental, that they spread no farther. In view of this situation the studies of the inheritance of otosclerosis which are based upon clinical observations are of doubtful validity.

*Aural rehabilitation.*—A great deal of attention has been given to the problem of the treatment of those suffering war injuries to the ear. For the most part the program follows outlines already formed in civil life for the conservation and rehabilitation of hearing (22, 23). Vocational training is an important measure when the loss of hearing unfits the person for his former occupation. The prescription of hearing aids, the teaching of lipreading, and speech correction are employed wherever necessary (24). Special attention must be given to the psychological problems presented by the sensory defect (25, 26). It is necessary to train a person in the best use of a hearing aid, and even those who have worn such a device for a year or more can profit from this tutelage (27).

The increased interest in hearing aids has led to many studies of their performance from an engineering standpoint. Methods are being improved for evaluating their performance (28, 29, 30), especially with regard to the effects produced by the wearer himself (31, 32).

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## METABOLIC FUNCTIONS OF THE ENDOCRINE GLANDS

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It is a truism today that science has rebuilt the modern world. Whether we like it or not, we live in an era in which events staggering to the imagination are rapidly becoming commonplace. Instantaneous communication, rapid transportation, air conditioning, and the control of insect pests have so modified the physical world that its habitable parts are greatly expanded. Medical research has accomplished miracles in the prevention and treatment of disease. The implications of these newly available facts for our civilization are being sought for by politicians (1), educators (2), and scientists (3). It is perhaps timely therefore to pause from the orderly collection and presentation of scientific facts in order to consider the trends established by the various divisions of science and to gain insight into the problems and opportunities of the new era.

Not only is the time ripe for a reevaluation of endocrinology, but also the slackening of research in this field during the war years has lessened the need for a review strictly confined to the publications of last year. For these reasons, the present review will concern itself with a series of topics which have been selected in the hope that they will illustrate some of the potentialities of endocrinology.

### HORMONES AND ENZYMES

Biologists have long been tantalized by the many similarities and equally intriguing lack of relationships between the enzymes and the hormones. For example, growth may be controlled by either growth hormone or vitamin A, oxygen consumption may be depressed by inhibition of the respiratory enzymes or by removal of the thyroid gland, and, within limits, the concentration of calcium in the blood may be regulated interchangeably by vitamin D or parathormone. On the other hand, little evidence has been forthcoming to support the thesis that symptoms of the deficiency diseases are brought about by a failure in formation or utilization of hormones.

The mechanisms by which the hormones exert their influences are by no means clear. Since the administration of hormones leads to increased growth and oxygen consumption, and since enzyme systems provide the machinery for energy transfers, it seems clear that administration of hormones increases the rate of enzymatic activity. The difficulty concerns the manner in which the increased rate of metabolism is brought about. One possibility, which has the advantage that it suggests a line of experimental attack, is that hormones cause an increased concentration or rate of reaction of the slowest member in a linked chain of enzymatic reactions. It becomes pertinent, therefore, to inquire whether administration of hormones leads to a demonstrable increase in concentration of an enzyme system or to conditions favoring increased enzymatic activity.

There seems to be no question but that a modified concentration of certain enzymes characterizes a variety of endocrine states. Greatly increased amounts of alkaline phosphatase are demonstrable in the blood of hyperparathyroid patients (4). The uterine epithelium from several animal species contains increased amounts of alkaline phosphatase during pregnancy (5). During early pregnancy, the syncytial trophoblast of the human placenta contains little of this enzyme, but toward the middle of gestation and at term large amounts are present (6). Alkaline phosphatase increases greatly in the liver of dogs made diabetic by alloxan (7). Acid phosphatase is not detectable in the endometrium of the nonpregnant sow and cat, whereas during pregnancy large quantities are contained in the cells of the deeply situated uterine glands (5). The high values of serum acid phosphatase which occur with prostatic carcinoma are increased by androgens and are depressed toward normal by the administration of estrogens (8). Likewise, estrogens lower the serum acid phosphatase and the alkaline phosphatase of bones in normal animals (9).

Oxidases have also been shown to vary in different endocrine conditions. The administration of thyroid hormone leads to increased oxygen consumption of the various organs and tissues, the rate and extent of change being characteristic for each. Moreover, changes in the respiratory quotient and other observations indicate that thyroid hormone alters the ability of cells to utilize certain metabolites (10). Treatment with extracts containing the thyrotropic principle causes the oxidases of the thyroid gland to increase

(11) and activation of the thyroid gland by exposure to cold entails a marked rise in the oxidation-reduction potential of the colloid (12). Moreover, both oxidase and peroxidase reactions have been described in the thyroid gland (13, 14) and both have been suggested to participate in the synthesis of the thyroid hormone. The adrenal cortex has also been found to influence the oxidase activity of various organs. The activity of cytochrome oxidase and the concentration of cytochrome-*c* decline after adrenalectomy and are restored by injection of adrenal cortical extract (15). On the other hand, an opposite effect is apparently induced in the skin, since hair growth and oxygen consumption increase after adrenalectomy (16). It has also been shown that melanogenesis is increased and the concentration of dopa oxidase raised in the skin of adrenalectomized rats (17).

Hertz (18) has recently described a close relationship between folic acid and the estrogens. Diets deficient in the vitamin caused an almost complete failure in growth of the chick oviduct after administration of stilbestrol. Debility resulting from deficiencies of other members of the B group did not affect the responses of the oviduct. The addition of crystalline folic acid to the deficient diet led to a quantitatively predictable response after stilbestrol injection.

The foregoing paragraphs amply document the hypothesis that the concentrations of certain enzymes are profoundly modified in states of altered endocrine activity. Considering the relatively few enzymes which have been investigated under conditions of different endocrine function, the results indicate an extremely rich field for exploration. Indeed, although the fragmentary results presently available are insufficient for generalization, the possibility exists that an altered endocrine balance may express its effects through modifications in the equilibrium between competing enzyme systems.

#### INHIBITORS OF HORMONES

The recent discovery of a series of drugs which prevent the formation of the thyroid hormone has opened a new chapter in thyroid physiology (19 to 22). Unlike previously known goiterogenic agents, these new compounds cause enlargement of the thyroid gland despite iodine administration. Histologically, the gland presents an appearance of extreme hyperplasia, but physiologically a decreased rate of secretion is manifested by an abrupt fall in the

basal metabolic rate (20, 21). The hyperplastic effects of the drugs are abolished by hypophysectomy or by the administration of thyroid hormone (20, 21, 23). The antithyroid drugs do not interfere with the action of thyroid hormone, since the basal metabolic rate may be maintained at normal or supernormal values despite the simultaneous administration of full doses of the inhibitory compounds. These facts strongly suggest that the synthesis of thyroid hormone is prevented by the antithyroid drugs. The thyroid enlargement is to be regarded as compensatory hyperplasia resulting from the overactivity of the pituitary thyrotropic hormone which, in turn, is caused by the release of the pituitary gland from thyroid inhibition (20, 21).

The demonstration that antithyroid drugs stop production of the thyroid hormone has suggested procedures for analyzing the synthetic steps in formation of the hormone. Following Harington's discovery of and characterization of thyroxine (24), a controversy which is still unresolved has centered around the nature of the natural hormone. On the one hand, extracts containing the active principle from the thyroid gland contain thyroxine bound as a globulin and not in the free form (25). On the other hand, although exceedingly delicate tests for it exist, thyroglobulin has not been demonstrated in the blood stream (25, 26, 27), suggesting that the storage form is chemically different from the circulating form. The problem does not concern us here, however, since either dried thyroid or crystalline thyroxine effectively prevents the hyperplastic effects of antithyroid compounds, thus indicating that the block in synthesis of the thyroid hormone is at a stage prior to the formation of thyroxine. On the assumption that thyroxine synthesis proceeds through the ethereal coupling of two molecules of diiodotyrosine with elimination of one of the alanine side chains Dempsey & Astwood (23) tested the effectiveness of diiodotyrosine in preventing hyperplasia of the thyroid gland after the administration of thiouracil. It proved to be almost totally ineffective. It seems reasonable therefore to postulate that the antithyroid drugs interfere with this step in thyroid synthesis if such synthesis involves the coupling of diiodotyrosine (13). On the other hand, there is excellent evidence that thiouracil prevents the normal uptake of iodine by the thyroid gland. Astwood & Bissell (28) have demonstrated a sharp decline in iodine concentration of the thyroid gland after administration of thiouracil, and there is general agree-

ment that the thyroid uptake of radio-iodine is depressed by anti-thyroid drugs (29 to 32). Notwithstanding these observations, the ability of the thyroid to accumulate iodine under antithyroid treatment sufficient to block the formation of active hormone has been demonstrated *in vivo* by the administration of massive doses of iodine (33) and *in vitro* by inhibition with sulfanilamide and azide (34). Although the efforts cited above have not yet led to satisfactory insight into the metabolism of the thyroid hormone, the amount of interest in the problem and the methods of attack seem to promise considerable advance.

A recent discovery somewhat analogous to that of the antithyroid drugs has considerably furthered understanding of pancreatic diabetes. In 1943, Dunn, Sheehan & McLetchie (35) described a necrosis of the pancreatic islets and a severe irreversible diabetes after the administration of alloxan. A single dose of the drug has caused an initial hyperglycemia, a transient hypoglycemia lasting about twenty-four hours, and, finally, a permanent elevation in the blood sugar level (36, 37, 38). It has been suggested that the initial hyperglycemia might be caused by adrenal stimulation, since typical epinephrine-type blood pressure curves were recorded after injection of alloxan (37) and since adrenalectomized rabbits injected with alloxan did not develop the initial hyperglycemia (39). This hypothesis has been refuted by experiments using dogs in which typical hyperglycemic reactions were obtained after adrenalectomy or adrenal denervation (38). A similar lack of agreement concerns the mechanism producing the temporary hypoglycemia. Since alloxan itself did not depress the blood sugar in surgically pancreatectomized animals (i. e., alloxan did not have an insulin-like effect), Goldner & Gomori (39) regarded the hypoglycemia as caused by the insulin liberated from degenerating islet cells. This concept too has been denied by Houssay, Orias & Sara (38), who demonstrated the secondary hypoglycemia in recently pancreatectomized but not in hepatectomized dogs. There seems to be general agreement that the final and permanent rise in blood sugar is caused by islet cell destruction, although the extreme hyperglycemia of alloxan diabetes suggests that the drug may also affect the liver directly (38, 39).

Histological studies of the pancreas after poisoning with alloxan have revealed an immediate degranulation and later degeneration of the beta cells. The alpha cells remain unaffected (36). This

observation fortifies the hypothesis, derived from earlier studies of the pathological changes in clinical diabetes, that insulin is secreted by the beta cells. The observation also paves the way for studies of the possible function of the alpha cells. Since in surgical pancreatectomy all varieties of the island cells are removed, whereas in alloxan diabetes the beta cells are selectively destroyed, it should be possible to ascribe to the alpha cells any differences between surgical diabetes and the diabetes induced by alloxan. Experiments along this line have shown ketosis to be absent, and the insulin requirement to be high, in dogs made diabetic by alloxan (40). The elevated requirement for insulin is similar to that seen in diabetes induced by the administration of adrenal steroids (41).

The foregoing paragraphs indicate how the discovery of thiouracil and of alloxan has stimulated research on the physiology of the thyroid gland and islands of Langerhans respectively. Moreover, they illuminate the general question of how valuable such pharmacological methods can be for solving purely endocrine problems. Since both discoveries were made empirically by fortuitous observations, no hypothesis has so far appeared to guide the search for agents to suppress the activity of other endocrine glands. Nevertheless, since antiendocrine activity may be regarded as an example of selective toxicity, and since a rich and varied selection of toxic agents is known, it seems not unreasonable to hope that new agents acting upon other glands and organs will be discovered.

#### HORMONES AND ANTIBODIES

It is fortunate that endocrinologists have become accustomed to mechanisms governed by the secretions of glands remotely located in the body, and to nicely balanced regulating systems, since otherwise the relationships between the endocrine organs and antibody formation could only prove so complex as to seem fantastic. Nevertheless, a brilliant series of investigations has shown, step by step, that the pituitary gland, operating through its control over the secretions of the adrenal cortex, regulates the functional activity of lymphoid tissue which in turn produces the gamma globulin or antibody-containing fraction of the plasma proteins.

The individual links in this chain of regulating factors have been known for varying lengths of time. Smith & Engle (42) in 1927 demonstrated unequivocally that the functional integrity of the adrenal cortex is controlled by the secretions of the anterior



lobe of the pituitary gland. Somewhat later, Selye (43) showed that atrophy of the thymus and other lymphatic organs occurred in various conditions of stress, and that this atrophy does not occur in hypophysectomized or adrenalectomized animals. Moreover, lymphatic degeneration may easily and promptly be induced by injections of adrenocorticotrophic hormone into normal, but not into adrenalectomized, animals or by administration of corticosterone (44). The effect does not occur after injection of other protein substances or other adrenal fractions such as desoxycorticosterone. The atrophy of the lymphatic tissue is accompanied by a lymphopenia, apparently caused by a failure to deliver an adequate number of lymphocytes to the circulating blood (44, 45, 46). Histologically the depletion of the lymphatic stores is caused by the dissolution and liquefaction of the stored lymphocytes (45).

The observations recounted in the previous paragraph establish that the pituitary adrenocorticotrophic hormone, through its activation of adrenal secretion, leads to dissolution and liquefaction of large numbers of lymphocytes. It remains to be shown that the lymphatic degeneration releases gamma globulins and formed antibodies into the circulating blood, and that the concentrations of these latter substances may be altered by administration of hormones.

White & Dougherty (47) have recently shown that injections of adrenocorticotrophic hormone cause an increase in the total serum proteins, whereas adrenalectomy leads to lowered serum proteins. Electrophoretic studies led to the conclusion that the increase is largely in the beta and gamma globulin fractions. Moreover, examination of the extracts of washed lysed lymphocytes revealed a protein component with the same electrophoretic mobility as that of the serum gamma globulin. A similar conclusion was reached after experiments utilizing the procedures of immunology (48). It can be concluded, therefore, that the lymphocytes contain a reserve store of gamma globulin and that the rate of release of this protein is under the physiological control of the pituitary gland which exerts its influence through the secretions of the adrenal cortex.

The last link in the chain connecting the pituitary gland with antibody formation consists of the demonstration that antibodies occur in the gamma globulin fraction of the plasma proteins, and that antibody formation and concentration may be influenced by

endocrine means. The identification of antibodies in the gamma globulin fraction is so well known as to require little comment. The most recent application of this knowledge has been the preparation of measles antibody from pooled plasma by physical chemical methods (49). The second part of the demonstration, that the rate of antibody release from the lymphoid tissue is under pituitary and adrenal control, has recently been accomplished by Dougherty, Chase & White (50). With this link, the chain connecting the pituitary gland to antibody formation and release has been completely forged.

#### HISTOCHEMISTRY OF ENDOCRINE GLANDS

In recent years several hormones have yielded the secrets of their structural formulae, while still others may be chemically characterized in partial fashion. Thus, a considerable degree of chemical insight attends our knowledge of the steroid hormones and of the active principle of the thyroid gland. Several of the pituitary hormones have been prepared in biological purity, and although their structural formulae are unknown, a considerable body of information has been accumulated bearing on their isoelectric points and the products of their hydrolysis (51). The accumulated knowledge of the chemical behavior of the hormones has led to several attempts to detect the location of the active principles in the cells of the endocrine glands.

Perhaps the greatest success in these efforts to devise histochemical reactions for the hormones has been attained with the steroidal compounds. The steroids, which are secreted by the adrenal cortex, ovary, testis, and placenta, are all alike in that they contain a cyclopentenophenanthrene nucleus. The various compounds which have diverse biological effects differ in the kind and location of different side groupings and in the degree of saturation of the nucleus. The biological activity seems, for the most part, to be associated with unsaturation and with hydroxy- or keto-groupings. Reasoning that ketone reactions, coupled with solubility tests, should reveal the location of the ketosteroids, Bennett (52) found that the outer layer of the fasciculata in the adrenal cortex of the cat contains acetone-soluble materials which form phenylhydrazones and semicarbazides. He showed also that the lipoids in this area are capable of reducing alkaline silver. The intracellular lipoidal droplets were frequently birefringent, and, on reaction

with digitonin, anisotropic crystals were formed. Since these reactions are characteristic of the ketosteroids and since they were negative in regions of the adrenal cortex other than the outer layer of the fasciculata, Bennett concluded that this zone represents the site of origin and secretion of the adrenal cortical hormones. Subsequently, the phenylhydrazine reaction has been applied to the mammalian testis (53) where phenylhydrazones are formed in the interstitial cells, to the rat's ovary, where the reacting substances are restricted to thecal, luteal, and interstitial cells (54), and to the human placenta where positive reactions have been observed in the syncytial trophoblast (55).

Bennett's conclusions were severely criticized by Gomori (56), who pointed out that the phenylhydrazones formed after treatment with phenylhydrazine were superimposable upon the results obtained by the plasmal reaction of Feulgen & Voit (57). The plasmal reaction involves the recolorization of leucofuchsin, which, under the name of Schiff's reagent, is commonly employed as a test for aldehydes. Feulgen & Voit (57), Verne (58), and Gomori (56) regard the test as indicating the presence of the aldehydes of fatty acids. However, it has not been possible to oxidize fatty acids by oxidations as mild as those which are effective in the plasmal reaction, and Lison (59) in a comprehensive study found that positive reactions with Schiff's reagent could be obtained with aldehydes, certain ketones, and even by some unsaturated compounds which contained no carbonyl grouping. Moreover, the carbonyl group in some steroids is active enough to react with phenylhydrazine (52), Schiff's reagent (60), and silver in alkaline solution (61). It therefore appears that these reactions, commonly employed to detect aldehydes, are not capable of differentiating between aldehydes and ketosteroids. Yet accessory evidence to be presented below indicates that, at least in the adrenal gland, ovary, testis, and placenta, positive phenylhydrazine reactions occur in the same locations which also exhibit other steroid reactions and are therefore indicative of steroid substances.

Among other characteristic reactions of the steroid hormones, their fluorescence (61, 62), their ability to form spherocrystals, their reaction with digitonin to form crystals which are anisotropic (63), and their response to the Liebermann-Burchardt test are noteworthy. These procedures have been applied to the ovary (54), testis (53), and placenta (60). In brief, positive reactions have been

obtained in the same locations which also contain substances reacting with phenylhydrazine and Schiff's reagent.

Since each of the reactions indicates more or less directly the presence of steroid substances, and since the physical and chemical bases of the reactions are quite different, it seems clear that the correspondence between the reactions reinforces the conclusion that the regions which give positive reactions are the regions in which the biologically active steroids are present. Conversely, it seems even more certain that the regions in which the reactions are negative do not contain these hormones in appreciable amounts.

The correlation of the steroid reactions described above with different physiological states has so far been done only fragmentarily. Sarason (64) has reported that the sudanophilic and birefringent zone of the adrenal cortex decreases in thickness after hypophysectomy. The changes in the adrenal gland during the alarm reaction have been investigated by Popjak (65). In moderate stress there is an increase in the phenylhydrazine reaction, whereas during severe stress a depletion of the substances which form phenylhydrazones occurs. These results have been confirmed in this laboratory (Deane, unpublished experiments) for both hypophysectomized rats and rats subjected to cold environments. The changes observed after these experimental procedures may be detected with the Schiff reaction, the phenylhydrazine reaction, or by observing the fluorescence or birefringence of the gland. For the ovary of the rat, Dempsey & Bassett (54) described the onset of the various reactions at approximately the time at which the Graafian follicle develops its antrum. They also called attention to changes in the reactions which occur during the lifetime of the corpus luteum, but made no detailed analysis of these changes in reference to the physiological cycle of the ovary. Everett (66) has recently correlated the Liebermann-Burchardt reaction with the stage of the reproductive cycle in rats and has shown that a marked change in the reactivity of the corpus luteum of the previous cycle normally occurs just prior to ovulation. In rats persistently in estrus, in which ovulation does not spontaneously occur, there is an almost complete deficiency in the reactive material of the corpus luteum. Since Everett has previously shown that rats persistently in estrus fail to ovulate because of a preovulatory deficiency of progesterone, there is presumptive evidence that the Liebermann-Burchardt reaction somehow serves as an index of progesterone formation and secretion. This very promising lead

should be investigated further. So far as the testis is concerned, relatively little is known. Talbot & Dempsey (67) have found little or no birefringent lipids in the interstitial cells of infants and young boys, whereas considerable amounts occur in the Leydig cells of adult men. In one case of marked sexual precocity, birefringent lipids were observed in the testis of a child. Conversely, birefringence of the testicular lipids was decreased or absent in several cases of hypogonadism.

Before passing from the subject of the steroid reactions, it may be appropriate to mention a valuable improvement on the phenylhydrazine hydrochloride method of Bennett which has been worked out in this laboratory by M. Pechet, but which has not yet been published. This method involves the use of 2, 4-dinitrophenylhydrazine sulfate in phosphate buffer at pH 6.0 to 6.8. The phenylhydrazones formed with this compound are much deeper in color than are those formed after treatment with phenylhydrazine hydrochloride. In consequence, thinner sections can be prepared and better localization of the reactive substances is possible than following the previous method. Moreover, the nitro-derivative reacts more energetically than does phenylhydrazine, a circumstance which has been utilized to advantage in identifying the less reactive carbonyl groups in sections of the adrenal cortex by the combined use of the hydrochloride and the nitro-derivative. The procedure devised involves treatment of the section with phenylhydrazine hydrochloride until the more reactive groups are combined, followed by subsequent immersion in a solution of 2, 4-dinitrophenylhydrazine sulfate. The red dinitrophenylhydrazone may be differentiated from the yellow phenylhydrazone by virtue of the difference in their colors.

The presence of a large percentage of iodine in the active principle from the thyroid gland has long attracted the attention of histochemists. Until recently the results from procedures designed to place this iodine in evidence have remained unconvincing (68, 69). In recent years, however, data of more critical value have been derived from three separate methods. These procedures consist in the localization of administered radioactive iodine by means of radioautographs of sectioned thyroid glands (70), in the detection of iodine-containing compounds in sections by their ultraviolet absorption spectra (71) and by their opacity to soft x-rays (72). In addition to this evidence for the iodine content, a number of other histochemical procedures have been applied to the thyroid gland

and have provided information concerning its autofluorescence and content of oxidative enzymes (13), as well as its metachromatic and other staining properties (73).

The cytological methods commonly used as pituitary stains have not contributed materially to an understanding of the chemical milieu of the gland. However, in recent years the Bodian protargol reaction has been applied to the pituitary gland and it has been shown that some of the gland cells contain granules which are impregnated by silver (74, 75). This method, involving the fixation of silver salts by tissue elements and a subsequent reduction of the silver from its salt, appears susceptible to comprehension from a chemical viewpoint, since it should be possible to determine the nature of the argyrophilic compounds. In addition to their ability to reduce silver in Bodian's method, some of the pituitary cells also stain intensely with basic dyes. This cytoplasmic basophilia is abolished in sections incubated in solutions of crude (76) or crystalline (6) ribonuclease, a circumstance which probably indicates a high concentration of ribonucleoproteins in these cells. This observation is of some interest in view of the general association between ribonucleoproteins and protein synthesis (77, 78).

For the sake of completeness in this account of histochemical observations on the endocrine glands it should be noted that reactions characteristic of polyphenols, and therefore of epinephrine, are easily obtainable in the adrenal medulla (79, 80). Moreover, secretory activation of the adrenal medulla by stimulation of the splanchnic nerves causes readily detectable changes in sections prepared by these methods (80).

#### EFFECTIVENESS OF HORMONES: END-ORGAN RESPONSIVENESS

The development of the subject of endocrinology, entailing the discovery and isolation of a multitude of biologically active substances with various metabolic effects, has posed many problems concerning the regulation of endocrine activity. There has been a strong tendency among endocrinologists to classify endocrine adjustments and endocrine diseases in terms of hyper- or hyposecretion. Thus Addison's disease is customarily attributed to too little adrenocortical activity, while Graves' disease suggests too great a production of thyroid hormone. This point of view has received strong support from both surgical and substitutional therapeutics, since many of the endocrine diseases have responded either to sur-



gical removal of the offending gland or to the administration of extra amounts of the active glandular principles. Yet, from theoretical viewpoints, it should be remarked that endocrine malfunction may as easily be explained by assuming an altered responsiveness of the end organ. According to this latter thesis, a disease such as diabetes might be caused not by a deficiency in the quantity of, but by a peripheral refractoriness to, insulin. It is proposed to examine these two alternative theories in the following paragraphs in order to see whether critical evidence may be brought to bear for or against either or both.

The evidence for hypersecretion of the thyroid gland during hyperthyroidism is convincing. Histologically, the appearance of the thyroid gland is compatible with an increased release of colloid into the blood stream. The level of circulating blood iodine is increased (25) and the basal metabolic rate is high. Surgical removal of the gland causes a marked decrease in metabolic rate, a decrease which is paralleled by a concomitant fall in blood iodine. Finally, the daily thyroid hormone requirement in substitutional therapy is the same for previously hyperthyroid or previously myxedematous patients (25).

Measurement of the amounts of ketosteroids excreted in the urine provides evidence of hypersecretion of the adrenal cortex. In a case of virilism, for example, as much as 857 mg. ketosteroid per day has been detected (81).

On the other hand, there appears to be valid evidence that the sensitivity of the peripheral end organs may change under some conditions. For example, during acute starvation in the dog, prostatic secretion ordinarily decreases (82). This decrease is apparently caused by a deficient gonadotropic activity on the part of the pituitary gland, since the administration of gonadotropic extracts corrects the deficient response. Moreover, when castrated dogs are injected with a constant daily amount of androgen, and observed for the amount of prostatic secretion before, during, and after starvation, prostatic activity is definitely increased during the period of starving (82). The conclusion seems clear that withholding food leads to an increased sensitivity of the prostate to androgen.

In a series of experiments designed to test the sensitivity to estrogen of juvenile and mature rats and guinea pigs, Wilson & Young (83) observed a rapid increase in responsiveness which occurred during the first month of life. Moreover, the responsiveness to estrogens apparently can vary from animal to animal, and to a



degree sufficient to cause failure of normal reproductive function (84). Indeed, an enhanced sensitivity to estrogens which occurs during adolescence is well known. The threshold dose necessary to cause menstruation is high in the immature rhesus monkey (85). A given amount of estrogen causes greater perineal swelling in adult than in juvenile baboons (86). Wiesner (87) states that cornification of the vagina and enlargement of the uterus are not detectable within the first few days of postnatal life even when multiples of the physiological dose for pubescent rats are given. In addition to these changes associated with age, a seasonal variation in sensitivity has been reported (88).

The observations cited in the paragraphs above indicate that various endocrine situations may be characterized either by a changed rate of secretion of hormones or by an altered peripheral sensitivity or both. Consequently, an adequate description of endocrine phenomena requires an understanding of both rate of hormone production and of the degree of peripheral responsiveness. Insofar as is possible with present methods, these aspects of endocrine activity should be determined, and attention should be directed toward the development of new methods for the further elucidation of these endocrine mechanisms.

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## REPRODUCTION

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A number of reviewers in earlier volumes of this series have suggested that the various chapters might be more useful if, in different volumes, selected specific aspects of a subject were given critical analyses rather than adhering to the annual custom of considering the year's work in the entire field. In the past year reviews have appeared dealing with the origin of the germ cells (1), embryonic sexual development and intersexuality (2), behavior (3), metabolism and mechanism of action of gonadotrophins (4), lactation (5), the menopause (6), the adrenal-gonad relationship (7), the prostate gland (8), virilism in women (9), the ovary and menstruation (10), water balance in pregnancy (11), and the endocrinology of neoplastic diseases (12). In a general field as abundantly reviewed as this, a survey of the work of the past year may serve a function, even though limitation of space and the inaccessibility of certain foreign periodicals necessitate incompleteness.

### THE GERM CELLS

Further evidence that the ova in the postnatal rat arise from the germinal epithelium is the observation that the ova contained granules of ink after the germinal epithelium had been intravitaly stained with India ink (13). In a quantitative study (14) the loss of oocytes in the young prepubertal rat was striking, and atresia was a common finding; the formation of oocytes from cells in the germinal epithelium was also observed.

Glycolysis in spermatozoa is mediated by adenosinetriphosphate (15, 16), with the glycolytic pathways and enzymes involved in the anaerobic metabolism resembling those of other animal tissues (15); a close relationship exists between glycolysis and activity (15). Ram spermatozoa retain their original rate of respiration and motility even when washed free of seminal constituents and stored for several hours (17), and the addition of various seminal constituents to ejaculates failed to alter the life span of human spermatozoa (18). Ejaculated spermatozoa have a much lower rate of respiration and aerobic glycolysis (16) and are less

capable of withstanding adverse conditions (19) than epididymal spermatozoa. The steady decline in the resistance of spermatozoa as they pass along the excurrent ducts is attributed to changes inherent in the spermatozoa rather than in their environment (19). The increase in endogenous respiration of the spermatozoa in excised epididymides after storage is also regarded as an aspect of "maturation" of the spermatozoa (16). A large proportion of human spermatozoa survive from two to eight days at  $-196^{\circ}$  or  $-79^{\circ}\text{C}$ . when frozen in 1 cc. quantities (of semen), but not when frozen in minute amounts as films or in fine capillary tubes (20); this ability is not shared by spermatozoa of laboratory mammals. As might perhaps be expected, antigenic differences between the spermatozoa of different inbred strains of mice have been observed (21).

Although the sperm count is an important indicator of fertility or sterility, the number of abnormal spermatozoa may be a better criterion (22, 23), and it has been suggested that fertility may be present with sperm counts much lower than usually considered requisite (23). Of the female genital secretions, only that of the vagina decreased the life span of human spermatozoa (18), although the cervical mucus is considered to act as a selective filter of spermatozoa (24). Spermatozoa were found in the ovarian segments of 21 per cent of the uterine tubes of rats examined fifteen minutes after ejaculation, and in all after one hour (25). The number of tubal spermatozoa was exceedingly small, however, as compared to the number in the uterus. The long standing question of why enormous numbers of spermatozoa must be introduced into the female genital tract to effect fertilization of the ovum by a single spermatozoon may find an answer in an enzyme, hyaluronidase, present in sperm suspensions. Rowlands (26) has found that the addition of this enzyme to sperm suspensions greatly decreases the number of spermatozoa required for conceptions upon artificial insemination of the rabbit.

The possibility that defective spermatozoa may be to a large extent responsible for embryonic death or malformations is indicated by the high mortality and increased frequency of abnormal development in chick embryos developing in eggs fertilized by spermatozoa irradiated with Roentgen rays (27). Perhaps also consistent with this possibility is the report that when thirty women in barren marriages were artificially inseminated with

semen from their husbands four of the nine conceptions ended in miscarriage, whereas in fifteen such cases in which semen from outside donors was used eight of the ten resulting conceptions went to term (28).

The first polar body is apparently not formed by the ovum of the horse until after the egg is shed, a situation found elsewhere among mammals only in the dog (29). Phases of maturation and fertilization have been observed in two human tubal ova considered to be approximately twelve and twenty-four hours old (30), and fertilization with early cleavage of human ovarian ova has been achieved *in vitro* by Rock & Menkin (31). Although abortive parthenogenesis has been both reported and denied earlier, Kosin (32) found fifteen of one hundred blastodiscs of eggs laid by non-mated or virgin hens contained mitotic figures and two to four nuclei when studied in microscopic sections. Of interest is the observation that during the first half of the twelve hour period between insemination and fertilization in the rabbit one or both gametes can be fatally injured by raising the body temperature by 5° to 6°F. (33). Transuterine migration of the ovum has been found to be frequent in the sheep when a double pregnancy results from two ovulations in one ovary (34).

#### DEVELOPMENTAL PHENOMENA

In terms of normal events it has been found that sexual differentiation in the opossum occurs on the first day postpartum in some individuals, presumably males, and on the third day in the females and probably some males (35). In keeping with its short intrauterine life, the hamster exhibits a rapid rate of development of the genital system, which at birth is like that of the rat and mouse (36). In the females of this species a prostate gland appears at birth and is fairly well developed at six days, although adult females have not yet been reported to have prostates. The morphological aspects of testicular descent have been studied in the opossum (37), a particularly favorable species inasmuch as even the embryonic phases of the process take place after birth. The descent is accomplished by the seventy-seventh day, suggesting that androgen is not a factor in its major aspects in view of the evidence that testicular androgen is not produced before the one hundredth day. The development of the gubernaculum testis in this species is unlike that recently described in human embryos

(38). Although never present normally in the female opossum, the development of prostate glands has been induced in female pouch young by administration of androgens (39).

Observations hardly consistent with regulation of the direction of embryonic sexual differentiation by gonad hormones have been added. Estradiol benzoate has caused hypertrophy of both Müllerian ducts in female chick embryos, whereas normally the right duct regresses; testosterone propionate caused regression of both Müllerian ducts in females but not in males, in which regression is the normal event (40). Both estrogens and androgens have provoked hypertrophy of the Müllerian ducts in female embryos of the garter snake (41). No change was seen in the Müllerian ducts of newly metamorphosed frogs given pituitary implants that resulted in great hypertrophy of the gonads (42). Merely raising the incubation temperature has resulted in well developed bilateral Müllerian ducts in thirty-seven of sixty male chick embryos and in hypertrophy of the right Müllerian duct in seventeen of fifty female chick embryos (43). Inasmuch as the genital system in the presence of ovarian agenesis is completely female, despite its atrophic condition, it has been suggested (44) that embryonic differentiation of the human gonaducts progresses under genetic influence and independently of ovarian hormones. Moreover, the induction of female mating behavior in a rat with congenital absence of gonads has prompted the suggestion that the embryonic differentiation of central nervous mechanisms for copulatory behavior does not involve gonad hormones (45).

Five cases of true hermaphroditism in man have been reported in the past year (46, 47, 48), bringing the total number in the literature to thirty-five or thirty-six (49). Perhaps significantly, all of the five cases were lateral hermaphrodites or nearly so, resembling the usual situation in the rarely encountered hermaphroditic rodent. An additional case of hermaphroditism has been reported in the mouse (50), bringing the total in this much studied species to six. In an interesting race of hermaphrodite-producing pigeons (51) the male embryos show a delay in regression of the ovarian cortical tissue on the surface of the left testis (52). Genetic studies (51) indicate a nongenetic influence, tentatively identified as an unusually high level of maternal estrogen, as well as one or more genetic factors in the genesis of the hermaphrodites, which are modified males. Cell cords resembling early seminiferous tub-



ules have been found to occur commonly in the ovaries of the common western shrew (53).

What is probably the first case of arrhenoblastoma complicating pregnancy has been described (54). In a young woman masculinization became apparent during the third month of pregnancy. At term the right ovary was an arrhenoblastoma whose removal resulted in subsidence of the masculine changes. The child was normal except that the external genitalia indicated it to be a female pseudohermaphrodite.

#### THE HYPOPHYSIS

No parallelism exists in the growth rate of the hypophysis and of the testes in the cockerel (55), but a correlation was found between the curve of the potency of the hypophysis and that of testicular weight (56). As to effects of steroids upon the hypophysis, the estrogen employed and the strain of rat used clearly modify the degree of hypertrophy produced (57). In dwarf mice the administration of estrogens or testosterone causes the hypophysis cytologically to resemble a chromophobe adenoma, apparently by retarding the origin of other cell types from the chromophobes—the change in this direction being apparent within a few hours (58). The loss of cytoplasmic granules and increased vascularity of the rat's hypophysis under the influence of estrogens has been suggested to be associated with the possible increase in production of lactogen at the expense of other pituitary hormones (59, 60). Pellets of estradiol benzoate and stilbestrol in the hamster lead to proliferation of cells of the pars intermedia which invade the pars nervosa and reach the brain, in some cases invading the third ventricle. The cells of the supraoptic nucleus are severely damaged, while the paraventricular nucleus shows less change (61). When testosterone propionate in fairly large amounts was given to early postnatal rats the cellular pattern of the hypophysis of the females at 110 to 131 days of age closely resembled that of normal males; no significant effect was apparent in the males (62). Zondek (63) has reported that occasional rabbits carrying intra-uterine pellets of estrone may show evidence of high levels of certain hypophyseal hormones such as giantism, hypertrophic lactating breasts, and quite large ovaries composed entirely of luteal tissue. Some rabbits with estrone pellets in the peritoneal cavity have also become thyrotoxic. The cessation of cycles and decreased

ovarian size in thiamine-deficient rats is the result of inanition which diminishes the gonadotrophic function of the hypophysis (64). Restriction of the caloric intake of mice by one third results in the persistence of juvenile ovaries, castration phenomena in the uterus, and retardation of mammary development, all of which suggest a low level of gonadotrophin (65). Evidence has been presented that in the rabbit the secretion of the follicle stimulating and luteinizing hormones are under the direct regulation of the thyroid which mediates the effects of estrogen (66). In the rat, however, Janes (67) has suggested that whereas estrogen provokes the release of luteinizing hormone in the intact animal, it causes the release of follicle stimulating hormone after thyroidectomy.

#### THE MALE GENITAL SYSTEM

The rarely accessible, original paper of Berthold on the transplantation of testes has been made available in translation (68). Weight changes in the epididymis after castration and their correction by injected testosterone propionate indicate testicular secretion as early as the eighth day in the rat (69). Contrary to previous observations, Moore (70) has found that cryptorchidism leads to reduced androgen production in young rats, but that after longer periods of cryptorchidism and in older animals the seminal vesicles do not indicate diminished levels of androgen. Thyroidectomy in cockerels may result in reduced androgen production by the testes (71), and when rats are subjected to the same operation at birth the gonads and their dependent accessory organs show a striking subnormal development (72).

In contrast to the apparent situation in certain other species, vacuoles in the interstitial cells of Leydig in man appear to be related to degenerative processes rather than secretory activity (73). In the fish, *Callionymus lyra*, the development and regression of the conspicuous seasonal nuptial characters coincide with appropriate changes in the interstitial cells but not with changes in the spermatogenetic cycle (74). On the other hand, Moore (70) has suggested that his observations in cryptorchidized rats are compatible with the secretion of androgen by the tubular elements of the testes.

No relationship was found to exist between testicular weight of immature hypophysectomized rats given sixteen different steroids and intensity of production of spermatozoa (75). Among the substances most active in this respect were androstenediol dipropio-

nate, methylandrostenediol,  $\Delta^4$ -pregnenolone, methylandrostenediol, androstenediol, and dehydroisoandrosterone. Protection against testicular atrophy was entirely independent of the other main pharmacological activities of the compounds tested. The capacity of androgens to maintain and to restore spermatogenesis after hypophysectomy has been found by Smith (76) to operate in the monkey as well as in rodents, and stimulation of activity in the seminiferous epithelium by administered androgens has been described in the snake embryo (41). Important evidence that the spermatogenic action of androgens is direct has been obtained in the monkey by Smith (76) and in the rat by Dvoskin (77), who found intratesticular pellets of androgen to be effective, with instances of the effect being restricted to the tubules adjacent to the pellet, while more distant tubules were unaffected. An almost incredibly prompt and striking effect of  $\alpha$ -tocopherol upon spermatogenesis in man has been reported (78).

In an extensive study Swyer (79) has found that the human prostate gland grows slowly until puberty when its growth is quite rapid. The size of the prostate changes little between the thirtieth and forty-fifth years, after which it undergoes either atrophy or hyperplasia. The quantity of prostatic fluid in castrated dogs completely deprived of food for many days and given androgen is much greater than in castrated dogs given the same amount of androgen but maintained on a full diet (80). The degree of hypersecretion by the prostate of the starved dogs decreased when the animals were refed. During three weeks in which no food was given the prostate in immature castrated dogs given androgen grew approximately 400 per cent. Probably the first observations showing that the prostate discharges before the seminal vesicles during ejaculation have been reported by Huggins & McDonald (81). Fractionated collections of human semen were made in three glasses as ejaculated. The characteristic constituents of prostatic fluid, fibrinolysin and acid phosphatase, were present in largest amounts in the first glass, while glucose, the characteristic component of the secretion of the seminal vesicles, was greatest in the third glass.

#### THE FEMALE GENITAL SYSTEM

Evidence as to the time of ovulation in the primate continues to accumulate. Hartman (82) has summarized his extensive experience in recovering ova and young embryos in the monkey. Only 2 per cent of his animals have ovulated outside the period

between the eighth and sixteenth days of the cycle. Van Wagenen (83) has recorded ninety pregnancies in the monkey following mating periods of forty-eight hours during the midmenstrual cycle, the eleventh or twelfth day being common to all matings. Of these pregnancies, 32 per cent followed a single mating period. Two additional human tubal ova have been obtained by Hamilton (30), who suggests that all of the tubal ova thus far recovered indicate that ovulation had occurred fifteen to thirteen days before the next expected menses. The same time is indicated by the shift of basal body temperature as studied by Tompkins (84), who reports that coitus or artificial insemination at the time of the change in temperature results in a high incidence of conceptions. As a method of ascertaining whether ovulation has occurred, Karnaky (85) has suggested kymographic tracings of uterine contractions. In two hundred consecutive patients the pattern of the tracing corresponded with the endometrial pattern as seen in biopsy specimens. Characteristic changes occur in the electropotential during ovulation in the rat, but there is no correlation between the number of peaks and the number of ova (86).

Ovulation has been induced in anestrus sheep by the administration of pregnant mare serum (87, 88). In the cow pregnant mare serum has induced multiple ovulation, but only when given in the follicular phase of the cycle. An extract of horse pituitaries, on the other hand, caused ovulation of a single follicle within two days irrespective of the phase of the cycle (89). Additional cases of probable ovulation in women induced by gonadotrophic preparations have been reported (90, 91). Ovulation has occasionally been induced in anestrus sheep by stilbestrol (88).

The mode of action of estrogen upon the ovary has been studied by Williams (92, 93), who could find no evidence in short experiments that the action is indirect.

Important observations on the origin of the cells of the corpus luteum have been made by Corner (94) utilizing their content of alkaline phosphatase as an indicator. In the pig the thecal cells are heavily laden with this enzyme and the granulosa free of it. Since the corpora contain some cells with much and others with none of the enzyme, the luteal cells apparently are derived from both. Support for the probability that ovarian estrogen is produced by thecal cells may be found in tumors of these cells. Seventy-four such tumors have arisen, many of them after the

menopause, and usually accompanied by such estrogenic effects as hyperplastic changes in the endometrium and enlargement of the breasts (95, 96). The administration of pregnant mare serum to female mice (97) and rats (98) has provoked the secretion of androgen as judged by disappearance of the X-zone in the adrenals and stimulation of the prostate glands, respectively. Further evidence that ovarian androgen in the rat is secreted by thecal cells has been obtained (98). Bursting atresia of follicles has been found in sixty-one species of birds, and it is proposed that this is the usual method of elimination of eggs with a large quantity of yolk (99).

The amount of human cervical mucus has been found to increase during the preovulatory phase of the menstrual cycle, reaching a maximum at approximately the time of ovulation (24, 100). Before ovulation this material is clear and transparent; after ovulation it abruptly decreases in amount (24, 100) and becomes more opaque (24) as a result of its higher content of leucocytes and desquamated cervical cells. A defective secretion of cervical mucus may be one cause of sterility (perhaps largely related to the participation of this material in migration of spermatozoa). In any case, deficiency in cervical mucus in women with no other defect has been corrected by administration of estrogen, and conception has followed (24). Cyclic cervical phenomena are not limited to man, as shown by the observation that the condition of the cervix of the mouse is sometimes more reliable than vaginal smears as an indicator of estrus (101). Contrary to earlier observations made *in vitro*, the cervix of the guinea pig, rabbit, and cat contracts *in vivo* after intravenous injection of oxytocin (102); the threshold dose, however, is much higher than that for the cornua and the response is of much shorter duration.

The pattern of motility of the human uterus *in vivo* is being clarified. Moir (103) and Karnaky (85) in extensive studies have confirmed the report of Henry & Browne (104) that in the first half of the menstrual cycle the spontaneous contractions are irregular, small, and fairly frequent and that after ovulation the contractions are much larger and more prolonged. Moir (103) found also that unfractionated posterior pituitary extract causes a brisk reaction immediately before, during, or soon after menstruation; at other times the response was slow, especially during the latter half of the cycle. The nonpregnant uterus responded

consistently to the pressor fraction, but not at all to the oxytocic fraction. In early pregnancy the response to an unfractionated extract was weak unless abortion was in progress. As pregnancy progressed, the responsiveness to oxytocin increased and to pitressin decreased. In labors under continuous caudal analgesia uterine contractions are usually not disturbed when the analgesia ascends to the level of the sixth to the tenth thoracic segments of the cord; analgesia ascending above the fourth thoracic segment, however, usually interrupts labor (105). The responses to estrogen and progesterone given by the nuclei of the cells of the endometrial stroma in the monkey have been found to differ from those in the mouse. In the mouse progesterone provokes nuclear hypertrophy and estrogen is without effect (106); in the monkey progesterone alone has no effect, estrogen causes nuclear hypertrophy, while estrogen and progesterone together cause nuclear hypertrophy and a modification of the chromatin pattern of the nucleus (107).

Based on the parallelism between the number of Doderlein bacilli in the vagina of the human female and of Gram-positive organisms in the vagina of the rabbit and guinea pig on the one hand and the level of action of estrogen on the other, bacterial examination of the vagina has been proposed as a rapid method for evaluation of estrogen level (108). Hartman (109) has described many different and not generally recognized types of cells in the vaginal smear of the rat in the different stages of the cycle as revealed by a modification (110) of the Shorr stain.

An apparently new conception of menstruation has been developed by the Smiths. Menstrual "serum" has been found to contain a fibrinolytic enzyme and a toxin also found in venous blood during or immediately before the menses (111, 112). The toxin, which appears (113) to be identical with Menkin's necrosin, is thought to be a universal result of cellular injury. The suggestion is made (114) that regression of the secretory endometrium is accompanied by metabolic changes yielding the toxin which, in turn, may be the immediate cause of menstruation through vascular corrosion. Since the toxin is also present in toxemia of pregnancy, there may be a toxemia of menstruation—which has much in common with shock (114).

The long recognized relationship of the thyroid to the menstrual cycle has been rendered susceptible of experimental study by Engle (115) who has strikingly shown that the relationship

obtains in the monkey. Monkeys rendered hypothyroid by thyroidectomy or thiouracil exhibit an amenorrhea that is corrected by administration of thyroid. Ovariectomized, hypothyroid monkeys may not experience menses upon the termination of a course of treatment with estrogen unless thyroid is given.

#### PREGNANCY

The fall in concentration of various blood constituents during pregnancy may be merely the result of dilution of the blood, which, as shown by determinations of specific gravity, begins in early pregnancy and progresses gradually up to five to eight weeks before delivery (116). An increased requirement for riboflavin during pregnancy is shown by the appearance of signs of riboflavin deficiency during the last trimester in a series of women on a low dietary intake. The signs were absent before pregnancy, regressed shortly after delivery, and responded to supplements of riboflavin (117). Apparently there is also an increased susceptibility to poliomyelitis during pregnancy (118).

The role of the various hormones during pregnancy remains obscure, perhaps to a large extent because the identity and the time and degree of fluctuations in levels of these hormones are not yet known with certainty. The ovary is not essential for the continuation of pregnancy in man at least as early as two and one half months after conception (119). In the shrew the corpora lutea reach their maximum size about the middle of pregnancy and then regress rapidly, frequently disappearing before parturition (120).

In agreement with earlier work on urinary values, serum gonadotrophin rises sharply in pregnant women, reaching a peak between the fiftieth and sixty-fifth days of gestation; thereafter the level declines gradually (121). In the same series of women the pregnanediol values were rarely above 20 or below 6 mg. per twenty-four hours up to the sixty-fourth to the seventy-eighth days. Thereafter the level rose gradually to reach a peak at about two hundred and fifty days. The peak level was maintained in some individuals, but declined in others. Not always was there more than a slight decline within twenty-four hours of delivery. It is interesting that the ovaries are dispensable (119) before high levels of pregnanediol are attained. In the woman ovariectomized early in pregnancy (119) extremely low levels or no pregnanediol was excreted.

Since urinary hormones or hormone metabolites may possibly



represent physiologically unused hormones, various criteria of acting levels of various hormones constitute another, and perhaps equally valid, means of assessing the humoral environment of pregnancy. In the baboon the character of the perineum, as compared with that after injected steroids, suggests that large quantities of active estrogen and progestin and possibly some androgen are secreted throughout pregnancy (122). In this species and by this criterion the onset of labor might be due to a gradual diminution in estrogen about fourteen days before parturition, followed somewhat later by diminution in progestin. In the mouse, on the other hand, the structure of the endometrium of the nonpregnant cornua of unilaterally pregnant animals suggests a high level of progestin and a low level of estrogen during approximately the first eight days of pregnancy; after the ninth day the same criteria suggest quite a low level of progestin and a moderate level of estrogen (123). The failure of development of deciduomata upon traumatization of the nonpregnant cornua of the uterus of mice on the tenth day of pregnancy (124) is also consistent with a low level of progestin by this time. The problem is complicated, however, by the observation that administration of estrogen and progesterone, alone or simultaneously, does not promote the formation of deciduomata in such traumatized cornua (124). Inasmuch as pre-existing deciduomata in one cornu inhibit the formation of additional deciduomata when the contralateral cornu is traumatized in progesterone-treated, ovariectomized mice (125), it is possible that the absence of deciduomal responses in traumatized cornua of unilaterally pregnant mice is the result of a placental influence and is not necessarily an indication of a low level of progestin. With respect to the functions of the ovary during pregnancy, it has been observed that ovariectomy before the eleventh day in the rat causes decidual necrosis leading to death of the embryos; after the twelfth day ovariectomy causes partial abortion from failure of the uterine muscle to relax before the expanding uterine contents (126).

Relatively huge doses of estrogen are tolerated with no deleterious effects in pregnant monkeys (127) and in pregnant women, in whom approximately one hundred times as much stilbestrol in a single dose is required to produce nausea and vomiting as in nonpregnant women (128). On the strength of this observation, the report that a highly cornified vaginal smear during pregnancy,

presumably indicating increased estrogen, constitutes a certain indication of approaching abortion or miscarriage (129) raises the question of whether the estrogen level is itself sufficiently high in these patients to interfere with gestation; an altered threshold to estrogen is another possibility. In either event, the administration of progesterone or ethynyl testosterone (129) or the latter supplemented with mixed tocopherols and thyroid substance (130) has been effective in threatened or habitual abortion. Prolactin has also been successfully used in treating threatened abortion (131). The thyroid hormone has been found essential for the maintenance of pregnancy and for parturition in the rabbit (132).

Histochemical reactions in the human placenta indicate that the placental steroids are secreted in the syncytial trophoblast (133). In the rat the trophoblast is considered to be relatively nonsusceptible to agents causing death of the fetus; the decidua, on the other hand, shows necrosis after ovariectomy or the administration of estrone or pregnant mare serum (126).

The possibility that the findings in toxemias of pregnancy are essentially exaggerations of those of normal pregnancy, some of which have nothing to do with toxemia, has been stressed by Novak (134), who regards the renal vascular spasm as significant. Eclampsia is associated with a typical placental lesion of acute form characterized by disappearance of maternal circulation and corresponding necrosis in the villous tree; a less acute condition of the same type is associated with nephritic toxemia (135). In this connection it is interesting that the menstrual toxin and fibrinolytic enzyme of the Smiths are present in circulating blood in toxemia (111, 112). Although not present in the blood of non-pregnant women (136), histaminase rises to high levels during pregnancy (136, 137). A slower increase is indicative of probable abortion (137), and reduction to very low levels characterizes toxemia (136). The activity of the placental histaminase is inversely proportional to uterine efficiency during labor (136). Placental cholinesterase is greater in pre-eclampsics than in normal patients (138).

Tests for pregnancy continue to receive attention. The frog test has been found highly reliable (139, 140) and the care and breeding of the test animals has been described, with the low cost emphasized. Both this (141) and the Friedman test (142) have been successfully used with serum as well as urine. The two-hour

test with the rat has been found invalid (143), but the six hour test is said to be accurate (144). Hyperemia of the infantile rat's ovary is described as a highly accurate test in undisturbed pregnancies (145) and is also a satisfactory test for pregnancy in horses (146). Since prostigmin induces bleeding when delayed menstruation is not due to pregnancy, and is without this action during pregnancy, the use of this substance has been suggested as a test for pregnancy (147, 148).

#### MAMMARY GLANDS

In keeping with the well established growth-stimulating action of estrogens on the mammary gland, hypertrophy of the breast is not uncommon in men being treated with stilbestrol for prostatic carcinoma (149), and gynecomastia is common, unless preventive measures are taken, in men employed in the manufacture of stilbestrol (150). Species differences in the responses of the mammary glands to each of the steroid hormones appear to exist. In mice progesterone stimulates growth of mammary ducts, while in rats the same substance stimulates growth of ducts and acini (151). Neither testosterone propionate nor methyltestosterone stimulates mammary growth in mice (152), but ethynyltestosterone is a more active stimulant of mammary growth than estrone benzoate (153) although it causes no secretion (154).

Neither estrogen (155) nor ethynyltestosterone (153) elicits mammary growth in hypophysectomized rats, although both are effective in intact rats. A hypophysectomized rat in parabiosis with a nonhypophysectomized rat, however, shows mammary growth when estrogen is injected, the growth being greater when the intact partner is a female (156). Inasmuch as the hypophysis is apparently necessary for the stimulation of mammary growth by estrogen, it is interesting that implantation of hypophyses from rats carrying pellets of stilbestrol does not evoke mammary growth in hypophysectomized-castrated rats, although similar recipient animals show considerable mammary growth when the hypophyses from untreated rats are implanted (157). The injection of lactogen in large doses concurrently with estrogen has provoked mammary growth in hypophysectomized-castrated rats, comparable to that in intact rats given estrogen (155). Interestingly, lactogen given alone caused thickening of the duct system in hypophysectomized-castrated rats.

That the adrenal cortical hormones may be involved in mammary growth is suggested by the observation that a saline extract of ox anterior lobe had no effect in adrenalectomized rats but did evoke mammary growth in intact female but not male rats (158). No mammary growth occurs in thyroidectomized cows given stilbestrol until the myxedema is relieved by administration of thyroid or thyroprotein (159).

Since to date no single artificially supplied hormone or combination of hormones has stimulated mammary growth as rapid as that which occurs in normal pregnancy, it becomes important to analyze the situation during pregnancy. Whatever the factor or factors, they are not present in the serum of pregnant mares and pregnant women in sufficient concentration to cause mammary growth in rats (160). Leonard (161) has found in the rat that the ovaries, the placenta, and the hypophysis must be present during the second half of pregnancy if the mammary glands are to develop fully.

Full lactation has been induced with some regularity in nulliparous heifers and dry cows by the administration of several synthetic estrogens by a variety of routes (162 to 166). At the outset the mammary secretion induced was colostrum in nature, but it gradually changed to milk of good quality (167), although the freezing point was persistently higher than that of normal milk (168). As might be expected, the milk from estrogenized cattle contains some estrogen (169). Simultaneous administration of synthetic estrogens and anterior pituitary extracts induced lactation in virgin goats sooner than estrogen alone (170). When prolonged administration of estrogens failed to induce lactation in cows and goats the administration of anterior pituitary extracts sometimes was followed by copious secretion of milk (170).

Crude extracts of ox hypophyses increase milk production during declining lactation in cows (171), but had no effect during the peak of lactation (172). Such preparations, however, exerted a galactopoietic effect at the peak of lactation induced by estrogen in heifers and goats (170). The galactopoietic activity was found to be greater in crude extracts of pituitaries of the horse than of the ox, while sheep and pig hypophyses showed little or no such activity (173). Since these results are not correlated with the relative prolactin content of the hypophyses of these species, prolactin is probably not the only or most important factor in such galacto-

poietic action (173). Milk production by lactating cows has also been increased by feeding iodinated ardein, which has high thyroid activity (174). The improvement in milk production produced by feeding iodinated casein is related to the stage of lactation, being slight in early lactation, highest during midlactation as production declines, and absent at the end of lactation (175). Milk from cows fed iodinated protein did not produce any elevation in basal metabolism, pulse rate, or blood pressure in young women (176).

Adrenalectomy on the fourth day of lactation in rats has caused great, but not complete, inhibition of lactation (177). In such animals lactation was partially maintained by administration of desoxycorticosterone acetate, and to a lesser extent by compound E. Compound A and cortical extract had deleterious effects on lactation. Termination of lactation, as well as its initiation, has followed the implantation of pellets of estrogens in cows (163). Adrenalectomized rats are more sensitive than intact rats to the inhibitory action of stilbestrol upon lactation (177). Of all of the steroids tested thus far, hexestrol dipropionate, when injected, is reported to be the most effective in inhibiting lactation in the human subject (178).

#### SEXUAL BEHAVIOR

Attempts to relate homosexual behavior to sex hormones have not been uniformly successful. In a series of twenty homosexual males the levels of urinary 17-ketosteroids and gonadotrophins were variable. In one half of these men the gonadotrophin level was less than in any normal male, and the low level could not be correlated with the 17-ketosteroid excretion or any physical finding (179). In one series of four eunuchoid homosexual males the administration of testosterone propionate converted all into normal males (180). In another series of eleven, however, only three reported benefit, while five reported intensification of their homosexual drive under treatment with testosterone and chorionic gonadotrophin (181). As an illustration of the complexity of the problem, Ellis (182) found in a review of the literature that the heterosexual libido and sex role of human hermaphrodites accord with a masculine or feminine upbringing and not primarily with their somatic characters.

The cerebral cortex is partially responsible for the sequential

timing of the separate estrous behavioral responses in female rats, extensive cortical destruction resulting in the loss of none of the discrete reactions but in a reduction of the biological effectiveness of the pattern as a whole (183). In the male rat, on the other hand, complete decortication permanently eliminated copulatory behavior; hemidecortication, however, was not always as effective. Noncopulating hemidecorticates could be reactivated sexually by large doses of testosterone propionate; after complete decortication copulation never occurred upon treatment with the same androgen (184). Nymphomania of long standing in a woman was found by Erickson (185) to be due to a neoplasm in the right paracentral lobule. Excision of the tumor abolished the nymphomania. Hemphill (186) has reported the restoration of virility following prefrontal leucotomy in a man with a long-standing obsessional neurosis accompanied by emaciation, impotence, hypogonadism, and low urinary 17-ketosteroids. It is assumed that the operation removed inhibitory influences on the hypothalamus or hypophysis.

In an ingenious study Benoit & Ott (187) have found that testicular growth in immature ducks is stimulated by green, yellow, orange-red, and red light when it falls upon the head (with or without the eye) or is directed upon the hypophysis, hypothalamus, or rhinencephalon through a quartz rod. Blue-violet light produced little testicular growth when external, but gave strong stimulation when conducted inside the head. By physical means it was found that red rays penetrate tissues while blue rays do not. Auditory stimulation may also modify reproductive phenomena, as indicated by an increased number of pregnancies, but also increased mortality of the newborn young, in rats repeatedly subjected to the sound of an air blast (188).

The observation that stimulation of the crop gland accompanies broodiness induced in ring doves by pellets of progesterone, desoxycorticosterone acetate, and testosterone propionate, but not of estrone, has led Riddle & Lahr (189) to attribute the broodiness to the stimulation of production of prolactin. Broodiness induced in cockerels by prolactin was found by Nalbandov (190) to be accompanied by evidence of depressed production of androgen. Both effects of prolactin were prevented by the simultaneous administration of the luteinizing hormone or of androgen, but not of follicle stimulating hormone. Nalbandov accordingly attrib-

utes broodiness in the chicken to deficiency in androgen or to an ovarian deficiency and not to prolactin *per se*.

#### GONADOTROPHINS

Serum gonadotrophin has now been purified by Rimington & Rowlands (191) to the point that the product assays 12,500 I.U. per mg. These authors do not agree that carbohydrate determinations can serve as a measure of potency of the active principle. The incorporation of various gonadotrophins into tannate pellets delays the absorption of the active material from subcutaneous sites (192). A delay in absorption is also considered to be the means by which insoluble metallic hydroxides increase the effectiveness of gonadotrophin from sheep hypophyses (193). Certain commercial anterior pituitary preparations have been found to exhibit posterior pituitary-like activity, suggesting contamination (194). The production of ovulation in the rabbit by extracts of certain plant juices is now attributed to their action in releasing hypophyseal gonadotrophin in the test animal (195). According to Bradbury (196), the rabbit has great limitations as a quantitative assay animal due to seasonal and individual variations.

The human ovary has responded to unfractionated sheep pituitary extract (90) and to the sequential and cyclic administration of equine and human chorionic gonadotrophin (91), although the state of the ovary at the time of treatment to a certain extent governs the nature of the response. Williams (197) finds no evidence for increased secretion of endogenous gonadotrophin following the administration of physiological doses of serum gonadotrophin to rats. Also in the rat, a basal condition of ovarian responsiveness to a single injection of 70 I.U. of gonadotrophin is attained seven days after hypophysectomy, and ovulation does not occur after the fourth day (198). The greater ovarian response to serum gonadotrophin in hypophysectomized rats carrying pellets of stilbestrol as compared with hypophysectomized rats given no estrogen is apparently the result of greater ovarian atrophy in the latter animals (199). A period of ovarian refractoriness to chorionic gonadotrophin in early pregnancy in the mouse is shown by failure of ovulation before the fourth day when amounts of gonadotrophin are administered that regularly induce ovulation after the fourth day of pregnancy (200).

Since the administration of prolactin beginning on the day of



vaginal estrus enables deciduomata to form in rats' uteri traumatized early in the resultant diestrus, it has been suggested that prolactin may be the pituitary hormone responsible for the start of luteal function after cervical stimulation (201). Also in the rat, lactogen appears to render functionally active corpora lutea formed under the influence of progesterone (202). Hisaw (203) has found that injections of chorionic gonadotrophin beginning in the latter half of the cycle delay menstruation in the monkey by continuing luteal function as shown by progestational endometria. Prolactin had neither effect. On the basis of these and other considerations, Hisaw suggests that the placenta, and not pituitary prolactin, is responsible for luteal functions, one of which is the production of estrogen, in early pregnancy.

In the forty day-old rat Simpson and co-workers (204) have presented important evidence that gonadotrophins do not maintain spermatogenesis by eliciting the production of androgen. The titers of gonadotrophins in the urine of men more than thirty years after castration have been found to be in the same range as those soon after castration of mature men or boys; presumably the high titers had been present for many years (205).

The possibility that antigonadotrophins may form in the human being upon extended treatment with various gonadotrophic preparations has been pointed out by Leathem (206). No antigonadotrophin was detectable, however, in the sera of patients treated sixty to one hundred fifty days with a combination of sheep pituitary extract and human chorionic gonadotrophin (207), despite the fact that the same treatment elicits the production of antihormones in the rabbit (208). Additional evidence that sera containing antigonadotrophins can inactivate endogenous gonadotrophins in the rat has been presented (209, 210). There is also good evidence now that the reaction between a gonadotrophin and its antihormone is a true immunological phenomenon (211) and that the antihormone is an antibody (212).

#### STEROIDS

The several factors that influence the rate of absorption of subcutaneously implanted pellets of steroids, most important of which is surface area, have been given detailed study (213, 214, 215). Both progesterone and anhydroxyprogesterone are clinically effective upon perlingual absorption (216). As a vehicle for the in-

travenous injection of fat soluble hormones, Friedman (217) recommends "Carbowax 1500," which is miscible with blood and dissolves steroids; no untoward effects have thus far been observed. Several steroids are also soluble in aqueous solutions of sodium dehydrocholate (218). When estrone is bound to glucoside its activity is greater perorally than parenterally (219). As for bioassays, a test for estrogen that gives a positive reaction to 0.02 cc. of blood from women in the middle of the cycle or to 0.5  $\mu$ g. of estradiol has been described (220).

Evidence that the liver is a site of metabolism of steroid hormones continues to accumulate. Transplantation of the rabbit's ovaries to the mesentery results in castration atrophy of the uterus although transplantation to the back muscles was followed by complete maintenance of the uterus (221). Pellets of progesterone placed in the mesentery of the rabbit had no effect upon the uterus, while subcutaneous and intramuscular pellets exerted their characteristic action (222). Liver pulp does not inactivate progesterone *in vitro*, however (221). Dietary hepatic injury impaired the inactivation of pellets of estrone in the spleens of rats (223). Perfusion of liver with estradiol and estrone led to progressive loss of activity in the perfusate (224) and to portions of the estrogenic activity appearing in the "estriol," "estrone," and "estradiol" fractions; perfusion with estriol resulted in activity in only the "estriol" fraction. The observation that intrasplenic pellets of estriol, equilenin, and  $\alpha$ - and  $\beta$ -dihydroequilenin in the guinea pig caused no fibromas has prompted the suggestion that these substances are inactivated by the liver as is estradiol, that they are derived from intrahepatic conversions, but are not end products (225). Aqueous acid extracts of beef liver inactivate both estrone and stilbestrol; alkaline extracts inactivate stilbestrol but not estrone (226).

The suggestion has been made (227) that the experiments taken to indicate inactivation of estrogens by the liver prove only that the liver prevents estrogen from entering the systemic circulation, which could be accomplished by biliary excretion and subsequent enterohepatic circulation. The finding (228) that most of the estrogen in the feces of pregnant cows is apparently estradiol, the only ovarian estrogen in the cow, appears to be consistent with this premise. On the other hand, fractionation of bile obtained from a dog given  $\alpha$ -estradiol intravenously showed that estradiol

was not its chief constituent; a ketonic estrogen, presumably estrone, predominated, with small amounts of a nonketonic estrogen, presumably estriol (229). Moreover, ligation of the common bile duct did not render the animal as sensitive to estrogen as hepatic damage produced by carbon tetrachloride (230). The kidney may also to some extent inactivate progesterone (222) and estradiol (224), apparently converting the latter to estrone. From a crude extract of potatoes with both estrinase and tyrosinase activity, a fraction containing tyrosinase free of estrinase was obtained, but estrinase free of tyrosinase was not achieved (231).

The observation that 17-ketosteroid excretion is less easily depressed by administration of methyltestosterone in patients with adrenogenital syndrome than in patients with Cushing's disease is regarded as further evidence that elevation in the former is a manifestation of a primary change, while in the latter it indicates a compensatory process (232). It has also been suggested (233) that the adrenals rather than the ovary may be the major source of the weakly phenolic ketone, "estrone," of urine.

The tonus of the human urinary bladder is increased by testosterone propionate (234), and stilbestrol greatly increased, while progesterone decreased, the peristaltic activity of the ureters of nonpregnant women (235). Nocturia, common in menopausal women with hot flashes, may frequently be relieved by treatment with testosterone propionate (236).

A large majority of three hundred forty-five patients with peripheral vascular disease have shown improvement when treated with estrogens (237). Treatment of older men with methyltestosterone significantly increased fusion frequency of flicker and the strength of the back muscle, with no effect on the maximum heart rate in exercise (238). Castration did not change the total cholinesterase activity of gastrocnemius muscle in the rat (239), and the synthesis of acetylcholine by frog brain tissue *in vitro* was depressed by adrenal cortical hormones, androgens, progesterone, and pregnanediol, while it was increased by estrone, estradiol, and pregnenolone (240). Stilbestrol may produce an inability to accommodate for near vision (241).

Local application of estradiol to the skin of hairless mice results in a generalized nonpitting cutaneous edema, the affected areas resembling the sex skin of monkeys (242). Stilbestrol produces deep pigmentation of the nipples, areolae, linea alba, and moles in

hypogonad girls and of the nipples in castrated male guinea pigs, even after adrenalectomy of the latter (243). Scrotal pigment is increased in the opossum and ground squirrel by androgen and in the opossum by estrogen (37).

Inasmuch as the remodeling of the pelvis in the girl occurs concurrently with other puberal changes, it seems probable that it has an endocrine basis (244). Resorption of the spongiosa at the ends of bones with little change in the shafts occurs during lactation in the rat, but not during pregnancy (245). Breeding accelerates skeletal ageing in female mice as compared with virgin females (246). Testosterone has a tendency to accelerate longitudinal bone growth in children, without hastening epiphyseal union (247). On the other hand, testosterone does not cause bone growth in the hypophysectomized rat, although it augments the action of pituitary growth hormone (248). Estradiol and an anterior pituitary extract oppose each other in their action on the growth of cartilage, but they cooperate in accelerating age changes in cartilage—the pituitary extract by stimulating osteoblastic bone formation and estrogen by promoting hyalinization of the marrow and inhibiting resorption of bone (249). Although stilbestrol and thyroxine have essentially opposite effects on endochondral bone formation in the rat, both retard the healing of fractures of the fibula, with stilbestrol having the greater effect (250). The degree of skeletal atrophy in rats produced by section of the brachial plexus is increased by castration and reduced by estradiol dipropionate (251). The frequent pelvic fractures in cows carrying pellets of estrogen results from persistent coital mimicry rather than rarefaction of bone, although loosening of the pelvic ligaments and a change in the pelvic angle may be disposing factors (252). The shortest interval for complete resorption of the medullary bone formed during egg production in the pigeon is twenty-two days; other morphological features indicate the resorption is primarily the result of decreased estrogen (253). The effects of estrogen on endosteal bone in this species are not modified by injection of thyroxine (254) or by parathyroidectomy (255).

Estradiol dipropionate is reported to incite a belated hypercalcemia in female guinea pigs that reaches its peak after thirty-five to fifty days' treatment; estradiol benzoate, however, had little effect (256). The striking increases in plasma calcium and inorganic phosphorus that accompany hyperossification in the pigeon (253)

at the time of egg laying (257) and under the influence of injected estrogens (258) are primarily in the nonultrafilterable fraction of both components. Estrogens also increase the lipid phosphorus and protein phosphorus in the plasma or serum of pigeons (254, 257) and chicks (259) and the serum cholesterol of chicks (259). When thyroxine is administered simultaneously with estrogen all of these blood changes are prevented in both the pigeon (254) and the chick (259). It is possible that the rise in plasma or serum calcium is due to the formation of organic phosphorus compounds (such as serum vitellin) that bind the calcium (257, 259); thyroxine is thought to prevent the rise by inhibiting the formation of these compounds or by causing their destruction (259). In rats stilbestrol and testosterone produced no change in serum calcium or in the output of calcium and phosphorus in the feces. Stilbestrol decreased serum phosphorus, the acid phosphatase of serum, and the alkaline phosphatase of the femurs, but did not alter the alkaline phosphatase of serum. Testosterone propionate had no effect on serum phosphorus or on the acid and alkaline phosphatases of the femurs, but increased the serum alkaline phosphatase of serum (260). The results of experiments employing radioactive phosphorus indicate that stilbestrol increases the rate of formation and utilization of phospholipid in birds (261, 262).

Contrary to previous thought, Albanese & Wangerin (263) find creatinuria in men is normal and not a feminine or prepuberal male characteristic. Unlike testosterone, methyltestosterone produces in man a creatinuria that, after a latent period of four to sixteen days, reaches a high level that is sustained as long as treatment is continued (264). The creatinuria is attributed to increased synthesis of creatine, an action not shared by testosterone propionate, although both may increase the amount stored. Methyltestosterone also provokes a creatinuria in hypothyroid patients (264). In thyrotoxic patients (265) testosterone propionate induces a strongly positive nitrogen balance and a gain in weight even when the caloric intake is less than the caloric expenditure. This substance also decreased the hypercreatinuria and improved the clinical condition of the patients. Methyltestosterone, however, increased the creatinuria and aggravated the toxicity; its effect on nitrogen balance was similar to that of testosterone propionate, but was not sustained.

The important observation by Smith (266, 267), that an oxi-

dative inactivation product of estrone stimulates the release of pituitary gonadotrophin as does estrone, and in much smaller doses, suggests that estrone exerts this effect indirectly through the formation of a similar compound. Figge (268) has reported that estrone inactivated by light, as judged by its failure to induce vaginal estrus in spayed rats, produces a longer vaginal estrus in intact rats than estrone, possibly by stimulating the production and release of gonadotrophin. Since stilbestrol unlike estrone, is equally effective in intact and castrated male rats in eliciting pituitary responses, it has been suggested that its action on the hypophysis must have a mechanism unlike that of estrone (269). The failure of estradiol and estrone, administered in many ways, to exert their characteristic action upon the uterus of eviscerated rats may be the result of the failure of the animal preparation to activate them (270). Similarly, estrone does not affect anaerobic glycolysis of the rat's uterus when added to the bath containing the uterus or when injected into the uterus immediately before excision, although an increase is shown in uteri removed from animals treated with estrone (271).

It is being increasingly realized that the target organ, as well as the quantity and identity of the stimulating hormone, is an important factor in governing the nature and intensity of the response. The much greater androgenicity of ethynyltestosterone in the mouse than in the capon (272) and the equality of effectiveness of estradiol benzoate and dipropionate on the plumage of the capon (273) are attributed by Caridroit to properties of the target organ. The water content of the uterus of the rat increases rapidly and then declines, despite the continued administration of the same dose of the same estrogen (274).

Many target organs vary at different ages in their responsiveness to steroid hormones. Deep pigmentation of the nipples and areolae, linea alba, and moles is produced by stilbestrol in hypogonad girls, but not in menopausal or postmenopausal women (243). Androgens induce the development of prostate glands in the female opossum, but this capacity seems to operate for less than thirty days after birth (39). The responsiveness to androgen shown by the accessory glands of reproduction in the male rat increases toward puberty (275). As in cattle, rabbits, and rats, the thyrotrophic potency of the hypophyses of mice is highest at puberty (276). Whether this is a factor in the puberal changes attributed

to androgen has not been determined. It has been suggested, however, that thyroidectomy decreases the responsiveness of the comb of the cockerel to androgen (71). "Folic acid" has been observed to be a striking factor in the responsiveness of the oviduct of the chick to stilbestrol (277, 278). "Folic acid" also greatly improves lactation in mice on purified diets (279). Biotin is one of the factors necessary for successful gestation and the birth of viable young, and it may be necessary for lactation (280). Metaplasia of the uterine epithelium under the influence of estrogen in the rat is decreased by extra vitamins B and C (281).

In addition to the properties inherent in the target organ, factors in its environment may participate in the response usually attributed entirely to the action of a hormone. This possibility is suggested by the observation that, as artificial vaginae, epithelium from skin of the thigh or from the vulva transforms into typical vaginal epithelium that stores glycogen and develops an acidity and a bacterial flora almost identical to those of the normal vagina (282) and from which cyclic vaginal smears may be obtained (283).

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## AVIATION PHYSIOLOGY\*

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When the reviewer accepted the invitation of the Editorial Committee in 1944 to prepare a review on Aviation Medicine for this volume, it was thought that some of the restricted and confidential material in this field would be reclassified and be available for this review. The work reported by Army, Navy, and civilian laboratories during the war years is a definite contribution to physiology. Only a few of these many reports have been published. Most of the unpublished material cannot possibly give aid or comfort to any of our enemies, past, present, or future. However, these reports cannot be used in this review. It is hoped that sometime soon this material may be made available through reclassification and publication.

It would be impossible and impractical to cover all subjects pertaining to aviation medicine for the *Annual Review of Physiology*. Therefore only the experimental work in four fields will be reviewed: anoxia, aeroembolism, acceleration, and oxygen equipment.

### ANOXIA

This discussion is divided into the various organ systems affected by anoxia.

*Respiratory systems.*—The respiratory needs of aviators have been discussed by Hall & Wilson (1). They measured the pulmonary ventilation of a group of resting and working men at various work levels and at various altitudes up to 40,000 feet. The method of determining the amount of oxygen used was to measure the drop in oxygen pressure in oxygen cylinders. The method is not the most exact approach to this problem but does give approximate

\* This review covers the period mainly from June 1944 to June 1945.

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results. The authors found that when adequate oxygen was supplied to the aviator, the pulmonary ventilation was the same as at ground level up to altitudes of 30,000 feet. At 40,000 feet, however, the pulmonary ventilation was greater for a given amount of work than at sea level. Therefore, the slight degree of anoxia experienced at 40,000 feet caused a greater pulmonary ventilation during work than at lower altitudes.

Many studies of alveolar air have been made on the anoxic subject. Helmholtz, Bateman & Boothby (2) have discussed some of these results. They note that the Army and Navy consider the partial pressures in the tracheal air for their requirements. The term "tracheal air" is used for the inhaled air saturated with water vapor at 37°C. Tracheal air is a static air unaffected by the gas exchange in the lungs. In contrast, alveolar air is affected by this exchange. Therefore, slight differences in results occurred when tracheal air was used in comparison to alveolar air. For example, when calculations were made to show how high an aviator could fly with oxygen without exceeding an altitude equivalent to 4,300 feet breathing atmospheric air, the tracheal oxygen calculations gave 35,700 feet, while the alveolar air equivalent was 36,800 feet. In this paper, the authors give an interesting graphic representation of water vapor, carbon dioxide, and oxygen in the alveolar air at various altitudes.

Harris (3) has studied the inspiratory tonus during anoxia by placing cats in a plethysmograph and recording the volume changes of the chest during reduction of oxygen in the inspired air. When the oxygen was reduced to 8 per cent (equivalent to 22,000 feet altitude) the volume of the cat's chest at the end of normal inspiration increased to three times that found at the end of a normal inspiration at sea level. He states that man at altitude without extra oxygen should form the habit of making forced expirations in order to relieve the tension on the inspiratory musculature. It has been noted frequently during anoxia that the subjects sigh and hyperventilate for short periods of time. These changes in respiratory activity tend to oppose the increase in inspiratory tonus.

*Blood.*—The question of the transfer of oxygen across the pulmonary membranes has been revived with the development of micro methods for the determination of oxygen tension in the blood. Comroe & Dripps (4) review this subject and report new experiments on the relationship of oxygen tension of arterial blood to

alveolar air. They note that the oxygen tensions of arterial blood reported in the literature for sea level range from 63 to 100 mm. Hg and the discrepancies between the alveolar oxygen tensions and arterial oxygen tensions range from 1 to 25 mm. Hg. Using a direct method for determining the tension of arterial blood, these authors report an average arterial oxygen tension of 97.1 mm. Hg at sea level while simultaneously collected alveolar air samples gave an average oxygen tension of 97.4 mm. Hg in samples taken at the end of expirations. Therefore, they conclude that there is no difference between alveolar and arterial oxygen tensions in resting subjects at sea level. It is not clear why the conclusions in this paper were all based on the end-expiratory alveolar air tension. Although the average figures did agree, some of the individual experiments showed marked disagreement. For example, in subject J. K., the alveolar oxygen tension at end-expiration was 86.2 mm. while the arterial oxygen pressure was 98.1 mm. Hg. In another experiment, the alveolar oxygen tension was 101.7 mm. Hg while the arterial was only 93 mm. The blood sample was drawn over several respiratory cycles and therefore the oxygen tension in the blood is probably more closely associated with an average alveolar air sample than an end-expiratory sample. A conclusion could have been drawn from these results that there are small differences between alveolar and arterial oxygen tensions as well as no differences as claimed by the authors.

Riley (5) has developed a method for determining oxygen and carbon dioxide tensions directly in blood in a Roughton-Scholar syringe. In eighteen determinations on arterial blood from men resting at sea level the carbon dioxide tensions varied between 32 and 41 mm. Hg (average, 38 mm. Hg) and the oxygen tensions varied between 93 and 110 mm. Hg (average, 100 mm. Hg). Lilienthal & Riley (6) have used this method to obtain the relationship of oxygen tension and oxygen saturations in the blood of man under normal conditions, anoxia, and reflex vasodilatation. For a given saturation the tensions fall close to those predicted by a standard oxygen hemoglobin dissociation curve (personal communication).

A paper of importance for experimental work in aviation medicine is that of Roughton, Darling & Root (7). These authors investigated the factors influencing the determination of the per cent oxygen saturation of the arterial blood. They found that in the

determination of the oxygen capacity of the blood by the usual tonometric technic there were (a) drainage errors, (b) gradual reversion of inactive pigment into active, and (c) traces of COHb in the blood. When these factors are taken into account, the average per cent saturation of normal man at sea level is 97 instead of 95 per cent as usually given in text books. They conclude that calculation of the arterial oxygen tension from saturations and the dissociation curve should only be used at altitudes above 10,000 feet. At lower altitudes on account of the shape of the curve and the errors in determining per cent saturation, the tensions should be determined directly. These conclusions focus attention on the methods for determining oxygen tensions of blood developed by Comroe & Riley.

Gemmill (8) has compared alveolar oxygen pressures and oxygen saturation of hemoglobin in subjects resting and carrying out muscular work at sea level and altitudes. He found that the alveolar oxygen tension and the saturation fell during work at altitude. The predicted tension from the blood saturation was less than the measured alveolar tension under these conditions. Therefore, under the stress of work and anoxia, there is a difference between the oxygen tension in the alveolar air and the arterial blood. The difference is probably due to an augmented pulmonary blood flow and an increased rate of oxygen intake which prevents the blood from becoming completely saturated during passage through the pulmonary vascular bed.

Lilienthal & Riley (9) have shown that samples of "capillary" blood taken from the heated ear have comparable oxygen saturations to those obtained by direct punctures of an artery. The results were checked at sea level and at altitude. The oxygen saturations of the blood obtained from the ear lobe at sea level with the subject breathing atmospheric air ranged from 94.3 to 97.7 per cent. Oxygen saturations of arterial blood drawn at the same time gave values varying from 94.8 to 98.3 per cent. These results demonstrate that the oxygen saturations of arterial blood may be obtained by microgasometric analysis of "capillary" blood. The results also substantiate the fundamental assumption in the oximeter method for determining oxygen saturations; namely, that the blood flowing in the heated ear lobe has the same oxygen saturation as the blood flowing in the arterial system.

Hemingway (10) has studied the oxygen saturation of a group

of men following mask removals at 35,000 feet. Using the ability to write as an end point, he found that this faculty ceased after fifty-five to eighty seconds of air breathing. At that time the average oxygen saturation as recorded by a Millikan oximeter was 56.6 per cent with variations from 45 to 67 per cent. These experiments show the difficulty of using blood saturation as an absolute measure of altitude tolerance when such wide variations are obtained in a group of men.

Aste-Salazar & Hurtado (11) have compared the affinity of hemoglobin for oxygen at sea level and at altitudes by studying the blood of twelve men at sea level and two hours after arrival at an altitude of 14,890 feet. They have also obtained blood for study from a group of natives who have lived at 14,890 feet and later from the same group following their first two hours at sea level. They found that there was a very slight decrease in affinity of the hemoglobin for oxygen in the group going from sea level to 14,890 feet while the blood from the natives did not change when they went from altitude to sea level. A good literature survey of this subject is included in their paper. It is of interest that a short stay of two hours at altitude changes the chemical properties of hemoglobin.

*Circulation.*—Graybiel, McFarland, Gates & Webster (12) analyzed the electrocardiograms obtained from 1,000 aviators. Their ages ranged from 20 to 30 years. The resting heart rates in this group varied from 38 to 110 with an average of 63.8. The P-R interval was found to vary between 0.09 to 0.28 second with an average of 0.154. There were sixteen cases with a P-R interval over 0.20 second. Other deviations from the normal standards were noted in this series. The authors conclude that the normal range extends well into the commonly accepted abnormal range. These results at sea level furnish the base line for altitude experiments. Harris & Randall (13) have made an experimental study of the electrocardiographic changes during anoxia. They took records by direct leads from the ventricles of dogs as well as by the standard leads. It was observed that there was no lengthening of the P-R interval or of the QRS complex down to a concentration of 8 per cent oxygen (22,000 feet). At 7 per cent oxygen, these intervals lengthen but there is cardiac dilatation and failure at this point. In the animal with a closed chest, there is a reduction in the height of the R wave which occurs at a level of 11 per cent oxygen (15,400

feet). The authors claim that this change is due to the increased respiratory distention of the chest and can be produced in a normal dog without anoxia by artificially inflating the chest. Comdr. A. Graybiel (MC) USNR (personal communication) states that these results do not apply to man since inflation of the chest does not produce similar changes in the R wave although there may be a considerable shift in the electrical axis.

*Digestive system.*—Van Liere and his group have continued their work on the effects of anoxia on the gastrointestinal tract (14). They found that partial pressures of oxygen of 94 mm. Hg in inhaled air had no effect on the motility of intestines of mice while lower pressures caused a significant decrease. The motility of the small intestine of the dog was not affected by partial pressures as low as 43 mm. Hg oxygen (32,000 feet). However, anoxia did produce a lowering of the height of contractions in the colon at partial pressures of oxygen from 110 to 94 mm. Hg (10,000 to 14,000 feet). If these results can be applied to man, it would mean that an aviator flying below 10,000 feet where he is not required to take any oxygen would not have any difficulty with the motility of small intestine and colon. In a later study, Van Liere, Northup & Stickney (15) combined the effects of cocaine and anoxia on dogs. In these experiments they found a marked decrease in propulsive motility of the small intestine, this fact showing that there was a synergistic action of the drug with anoxia. MacLachlan & Thacker (16) investigated the absorption of fat from the intestines of rats under anoxia. Following a fast, each rat was given 1.5 cc. of corn oil by stomach tube. The rats were exposed to partial pressures of oxygen simulating altitudes from 8,000 to 28,000 feet. The amount of fat remaining in the gut was determined and compared to the amount placed in the stomach to calculate the per cent absorption. At altitudes of 8,000 and 18,000 feet, no appreciable difference in fat absorption was noted. However, at 24,000 and 28,000 feet there was a decrease in fat absorption. The authors conclude that the threshold for an effect on fat absorption lies between 18,000 and 24,000 feet altitude.

*Eye.*—Gellhorn & Levin (17) have investigated the dilatation of the pupils in the eyes of cats exposed to barometric pressure changes equivalent to 25,000 feet or above. They conclude that this phenomenon is due to two components, (a) a diminution of tone of the third nerve center and (b) the formation of acid metab-

olites. McFarland, Halperin & Niven (18) have studied the changes occurring in visual thresholds during anoxia. Using a visual discriminometer which gives a precise control of intensity, wave length, and retinal location and duration of exposure, they were able to determine light thresholds against backgrounds of various intensities of illumination. Anoxia causes a definite decrease in differential brightness sensitivity. Changes were observed at 7,500 feet which became progressively greater as the altitude was increased. The changes were reversed by administering 100 per cent oxygen. These results demonstrate the importance of taking oxygen at 5,000 feet at night.

McFarland *et al.* (19) have used this same method to study the combined effects of anoxia and carbon monoxide on man. From their results, they calculate the increase in the physiological altitude in the presence of carbon monoxide. For example, at an actual altitude of 12,000 feet in the presence of 20 per cent COHb, the physiological altitude has been raised to 18,750 feet by the addition of COHb to the man's blood. Curves are presented for making similar calculations at various altitudes and for varying amounts of COHb in the blood. These results are very valuable in aviation physiology. The question is frequently raised as to the allowable amounts of carbon monoxide in the cockpit of a plane. It can easily be seen in the graphs of this paper that very small amounts of carbon monoxide in the blood of an aviator will place him in danger at altitudes less than 10,000 feet where he is not required to take oxygen. Their method of determining differential brightness sensitivity is the best quantitative method for determination of altitude tolerance that has been described at the present time. It should be used for many other problems in this field.

*Altitude tolerance.*—Many studies have been made in order to determine a man's anoxic tolerance and how this tolerance may be varied by physiological and pharmacological means. There seems to be a universal desire to discover a magic substance which will raise a man's ceiling. In all of this work, it must be kept in mind that the military services require the use of oxygen at 10,000 feet. A man with oxygen does not become severely anoxic until he flies at an altitude of 40,000 feet or above. Therefore any method of increasing altitude tolerance is not practical until the latter altitudes are reached. These studies, therefore, only apply to a relatively few aviators who fly to altitudes of 40,000 feet or above.



Altitude tolerance decreases with age in experimental animals (20), being greatest at time of birth. In mice (21) a slow rate of decompression, a diet of carrots, dehydration, and reduction of temperature increase altitude tolerance while starvation decreases this phenomenon. Various cholinergic and sympatholytic agents increase altitude tolerance while adrenergic and parasympatholytic agents augment anoxic effects (22). Therapeutic doses of the sulfonamide drugs produce small amounts of methemoglobin or sulfhemoglobin in blood of dogs (23). There was a slight reduction in arterial oxygen saturation. The changes are so small that it is safe to say that sulfonamides in dogs do not affect their altitude tolerance. Exposure of rats for several four hour periods during a month preceding tests show that the altitude tolerance of this group is increased (24). Thiouracil given to rats for six days increased their resistance to anoxia (25). Halstead (26) has reported changes in the dynamic visual fields during the third and fourth week following exposure to 10,000 feet altitude six hours a day and six days a week. The author concludes that regulations requiring the use of oxygen at 10,000 feet do not give adequate protection. It would be very rare in military service to have missions requiring such long flights every day over periods of weeks. However, it is possible that civilian air line pilots might be exposed to such conditions and changes in their visual fields should be looked for and prevented by the use of oxygen.

#### AEROEMBOLISM

A few papers have appeared in the general medical literature on aeroembolism during the past year. Bridge and his associates (27) have described the clinical signs and symptoms in a group of men exposed to 38,000 feet for ninety minutes in a low pressure chamber. The subjects did ten step-ups every five minutes during the ninety minutes in the chamber. In 167 man-runs, 50.9 per cent were terminated on account of joint pain, chokes, abdominal gas, or hyperventilation. There was a high incidence of pain in the anterior portion of the knee. There were post-"flight" symptoms in 15 per cent of all man-runs. Men working in low pressure chambers during routine indoctrination of cadets at high altitudes have seen these reactions in resting individuals. The important fact in this study is the high number of runs terminated when the subjects exercise at altitude. Goggio & Houck (28) have described a case

in which a man at 38,000 feet for thirty-eight minutes showed signs of collapse and was brought down to sea level. Fifteen hours later there was disorientation, aphasia, agraphia, and weakness of right facial muscles and of right arm and leg. By the end of the fifth day these neurological symptoms disappeared and he was discharged from the hospital on the ninth day. Fifteen days later he was readmitted to the hospital on account of "shakiness." At that time, he had a fine tremor of the right hand and weakness of the lower right side of the face. These symptoms persisted over a period of three months. This case illustrates a very severe reaction to an altitude run and the rare persistence of symptoms following the exposure to altitude. Brown and his associates (29) have also reported neurological reactions following exposure of man to altitude. They divide their cases into disturbances (*a*) of equilibrium and coordination, (*b*) of function of the large sensory and motor tracts, (*c*) of consciousness and cortical function, and (*d*) of subcortical mechanisms. There were also meningeal irritative phenomena, migraine-like attacks, and scattered nervous system changes of a minor character. These changes were seen on altitude runs given to 40,000 cadets in low pressure chambers at 30,000 feet for one hour followed by exposure to 38,000 feet for fifteen minutes. Rodbard (30) has noticed that men who had bends at 38,000 feet had immediate recurrence of the symptoms in the same anatomical location when reexposed quickly to the same altitude. This phenomenon depended on the time between the exposures, for bends did not reappear if 180 minutes elapsed between runs.

Harvey and his associates have published an important series of papers on the experimental production of air emboli. In the first paper (31) they describe that air bubbles rarely form in resting animals but do occur in blood vessels following muscular contraction or injury to the muscle. A theoretical discussion is given of the physical factors involved in bubble formation (31, 32). This work was continued by studying bubble formation in cats (33). The animal was prepared in a low pressure chamber in such a manner that the postcava could be observed for bubble formation during ascents to 45,000 or 50,000 feet. Even under these extreme conditions bubbles were rarely seen in resting animals; however, when the hind legs are stimulated, bubbles were frequently seen. Bubbles were also produced by injuring tissue (34). In the fifth paper (35) a study of the effects of denitrogenation on the nitro-

gen concentrations in blood of the postcava was described. The venous nitrogen fell in thirty minutes to a very low level and decreased very slowly after the initial rapid fall. Exercise increased the rate of fall.

This series of papers represent a valuable experimental approach to the subject of aeroembolism. From the practical aspect, however, they have added very little to what has not been already observed in man, for example, that oxygen breathing decreases the nitrogen content of the blood and that exercise increases the incidence of bends. It is also difficult to correlate results of animal experiments in which the animals under anesthesia are taken to 45,000 or 50,000 feet in order to elicit responses to what goes on in man not under anesthesia at lower altitudes.

#### ACCELERATION

The reviewer was discouraged about finding any published accounts of the work in this country on acceleration until the *Federation Proceedings* for March 1945 appeared. In that number, there were ten abstracts on this subject. Baldes & Porter (36, 37) have described the Mayo centrifuge which consists of two large flywheels and a carriage. The energy of rotation of the flywheels can be applied quickly to the superstructure which carries the man. This necessitates an adequate and quick clutching mechanism between the flywheel and the superstructure. The Mayo flywheels weigh 20 tons apiece. The reviewer does not agree with their statement that this type of construction is relatively simple and low in cost. Hall and his associates (38) have described briefly the Wright Field centrifuge. It consists of a turn-table 48 feet in length, having a cab on one end for a prone subject and one on the other end for a seated subject. The drive mechanism is controlled through a photoelectric system. The accelerating mechanism can rotate the cab from standstill to 90 miles an hour in ten seconds which produces 20 "g" in the cab. On this centrifuge Hallenbeck (39) has studied men following repeated exposures in order to see if an exposure is conditioned by previous runs. When subjects were exposed to a continuous sixty second exposure of 4.2 "g," six subjects who suffered loss of peripheral vision or blackout showed signs of improvement after the first ten seconds. When exposed to six ten second discontinuous runs there was an improvement in the second

and subsequent runs. The maximal time interval between runs was 29.1 seconds. It is difficult to see the practical application of this work for the time between dive bombing or gunnery runs would be much greater than that used in these experiments.

Sturm, Wood & Lambert (40) have developed a method for determining blood pressure of man while under "g" forces. They found with this instrument that the blood pressure at the level of the eyes fell 20 to 30 mm. per "g" increase in acceleration. The maximal fall occurred within seven seconds and recovered while the acceleration continued. Lambert (41) studied the physiological basis of "blackout" during acceleration on man. By applying external pressure to the eyeball during acceleration the threshold for blackout was lowered and by applying suction blackout was prevented. The authors conclude that loss of vision which occurs in acceleration without loss of consciousness is retinal in origin. This conclusion was reached by the Germans several years ago.

Code *et al.* (42) have described the physiological changes which occur in man during acceleration. These authors divide these changes into two phases, (a) the period of progressive failure and (b) the period of compensation. During the first period, the pulse rate increases, the amount of blood in the ear is reduced, the pulse in the ear may disappear, the blood pressure at the level of the base of the brain decreases, and there is reduction of vision and loss of consciousness. From six to eleven seconds after the onset of acceleration, the second phase begins. The blood pressure rises, the ear pulse returns, the pulse may slow, and recovery from loss of vision and loss of consciousness may take place in the man. It is doubtful if an aviator often has the opportunity to reach the second stage for the time during which he is subjected to "g" forces is generally less than six seconds. However, in tight turns it may last much longer and, in these cases, the compensatory phase would be of value. Lambert *et al.* (43) have also described the symptoms during acceleration. In the average individual, graying of vision occurs at 3 "g." Between 3 and 4 "g" peripheral vision is lost. Between 4 to 5 "g" vision is lost completely while above 5 "g" consciousness disappears. Code, Wood & Baldes (44) have used the Mayo centrifuge to determine the protection given by immersion in water. Immersion in water to the xyphoid gave 0.9 "g" protection, while immersion to the level of the third rib gave 1.7 "g" protection.

Water suits using this principle have been used in aviation but have not been very satisfactory. Wood, Clark & Lambert (45) have analyzed the protection given an aviator by a pneumatic anti-blackout suit. By using suits which applied pressure separately or together to the legs, thighs, abdomen, and arms, they were able to analyze the protection afforded by the single or multiple pressure combinations. They conclude that the most important site to apply the pressure is to the abdominal region. Pressure to the lower extremities has very little effect but in combination with abdominal pressure increased the protection by a factor of two. Therefore, pressure should be applied to both abdomen and legs for maximal protection against "g" forces.

#### OXYGEN EQUIPMENT

Gemmill (46) has described some of the physiological tests given to oxygen equipment. Tests are made at various altitudes with man (a) at rest at room temperature, (b) at work at room temperature, (c) at rest under cold conditions, and (d) at work under cold conditions. The altitude studies were made every 5,000 feet from 10,000 to 35,000 feet. From such tests, economy curves were constructed for the oxygen regulators for various altitudes.

Gagge, Allen & Marbarger (47) have described one of the most outstanding physiological developments of this war, pressure breathing. In 1941 experiments were conducted at Wright field which demonstrated that increasing the oxygen pressure in the lungs throughout the respiratory cycle by eight to twelve inches of water will allow some individuals to reach altitudes of 50,000 feet. From these observations, they developed a new type of oxygen equipment which raises the pressure in the lungs. The benefit that a man derives from pressure breathing is generally conceded to be due to the increase in partial pressure of oxygen in the lungs and the resultant rise in oxygen saturation of the blood. The authors are careful to point out that although nearly all trained individuals are able to tolerate eight inches of water pressure, above this amount circulatory failure may develop. Pressure breathing does not completely prevent anoxia above 43,000 feet. For example, at 45,000 feet and breathing against eight inches of water pressure, blood oxygen saturations are found which correspond to an individual breathing air at 15,000 feet. The authors

state that pressure breathing does not prevent bends and therefore does not take the place of pressurized cabins.

Marbarger, Taylor & Power (48) have measured the arterial saturations up to 50,000 feet. With 33 mm. Hg pressure above ambient, the arterial oxygen saturation was 76.4 per cent. This saturation corresponds to 16,000 feet while breathing air. There were slight changes in carbon dioxide content of the blood and pH indicating a loss of carbon dioxide from the body. In order to lower expiratory resistance, valves have been developed to give a high inspiratory and a relatively low expiratory mask pressure. Allen & Swann (49) have described such a valve and its operation. With the mask pressures set at 8.6 inches of water for the end of inspiration and 4.8 inches at the end of expiration, a subject at 45,000 feet had an oxygen saturation of his arterial blood of 90 per cent.

The standard altitude pressure tables published by Brombacher (50) are very useful in all pressure chamber experiments on oxygen equipment. Brombacher (51) has also published a critical account of methods for measurement of altitude of aircraft. A similar critical review is needed for measurement of altitude in low pressure chambers.

#### CONCLUSIONS

Some of the experimental work in four fields of aviation physiology is reviewed. Through intensive efforts of Army, Navy, and civilian laboratories several important and useful discoveries have been made in aviation physiology during the war years. Satisfactory oxygen regulators and masks have been developed through the cooperation of physiologists and engineers. Pressure breathing equipment has been perfected which enables some men to reach 50,000 feet. Anti-"g" suits have been devised for protection against the forces of acceleration. Another development has been the teaching of practical physiology to thousands of aviators. Lectures, demonstrations of the effects of altitude on man, and runs in the low pressure chambers have been given to nearly every aviator in our Army and Navy. The teaching of night vision is another example of applying physiology to large numbers of individuals. It is in these fields of instruction that physiologists have made their greatest contribution to aviation medicine in this war.

In contrast to these achievements there have been many dis-

appointments. No test has been devised for "bends" which will predict whether an individual is more or less susceptible to aerobolism than his partner. No practical substitute for oxygen has been discovered which will raise a man's altitude tolerance. We do know after four years of war much more about how man and animals react to altitude. Most of this knowledge has had no immediate practical value. However, the effort has not been wasted for some of this knowledge may be useful in clinical medicine in studying respiratory and circulatory diseases.



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## PHYSIOLOGICAL PSYCHOLOGY

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The current year in physiological psychology presents the unusual situation of having one of the largest accumulations of major research projects of any year to date, but with a large proportion of it still under military restrictions as to publication and therefore unavailable for review in the present volume. Fortunately we may be quite certain that most of this information is likely to be released within the next year or two, at which time we may obtain a much more adequate picture of the real progress in this field during the war years.

The lull in contemporary publications does however have the advantage of giving us time to integrate some of our previous detailed experimental findings into more systematic form and thus to provide a basis for the evaluation of further new findings. To cover such a broad systematic evaluation as well as the customary review of current literature the subtitle of the present review might well be "Biological Bases of Human Behavior," which implies that we shall be concerned primarily with attempts to understand both the general and individual determinants of effectiveness in human performances of all kinds. We shall therefore begin by a statement of a working hypothesis which is intended to represent the implicit assumptions underlying the work of most present day experimenters in this field.

Perhaps the most fundamental assumption in physiological psychology would be that which concerns the general nature of psychophysical relationships, a problem which philosophers still discuss under the name of the "mind-body problem" but which experimental psychologists have broken down into a number of subproblems more amenable to experimental investigation. Such subproblems would include hypotheses such as (a) the continuity or discrete nature of the subject matter of the physical, biological, and social sciences, (b) specific hypotheses as to the mode of functioning of the receptors, connectors, and effectors, (c) the relative importance of biological inheritance and environmental factors in determining individual differences in human abilities, and (d) the

effects of extreme working conditions upon effectiveness of human performance, especially under emergency conditions such as military necessity.

A general statement of current thinking on the nature of psychophysical relationships might be summarized in approximately this fashion: The subject matters of the physical, biological, and social sciences represent only rather arbitrary divisions on a basis of convenience as a division of labor among specialists. The field of knowledge is continuous and the three above-mentioned groups of sciences grade into one another by almost imperceptible variations, as shown in a study by Jones (1) by the fact that as a science matures it becomes more and more necessary to invoke the collaborative efforts of experts from a number of adjacent fields in order to provide an adequate understanding of the bridge areas between the older areas of science.

The progress of such collaborative efforts in integrating the descriptions of the various sciences leads us to believe that eventually all scientific descriptions will be analyzable or translatable into the same basic physicochemical terms. Nevertheless, the biological and social levels of description will continue to hold and develop their own usefulness for all ordinary purposes. These biological and social levels of description concern themselves with the properties of complex physicochemical organizations, in which the pattern of the organization often determines more of its properties than do the elementary materials of which they are composed. This concept, sometimes referred to as the doctrine of emergent evolution, has its counterpart in chemistry, where even a mirror image of a molecular pattern of a compound may have very markedly different physical and chemical properties from its counterpart.

To many persons outside psychology the idea of mental processes developing from purely physical processes may seem incomprehensible, but, we may ask, are the differences between conscious and nonconscious behavior any greater than the better known transformations of one physical form of energy to another, such as mechanical to thermal, radiant, or electrical energy? A part of the difficulty is merely linguistic, in that while these various forms of energy form a continuous physical series, the descriptive terminologies of pressure, heat, light, electricity, etc. were largely developed by persons working on only one form of energy without realizing that one could be transformed into the other.

Philosophers still struggling with the "mind body" problems

seem to have overlooked one or more of the following "jokers" involved, e.g.: (a) that the large apparent differences between mental and physical phenomena may not represent correspondingly great basic differences in terms of scientific analysis; (b) that if mental and physical phenomena are only two different aspects of the same general phenomena there is no great problem as to their "interaction" or their observed parallelism of temporal courses; (c) that often the apparent differences do not involve even different aspects of the same phenomena, but may represent only two more or less equivalent sets of descriptions in parallel scientific terminologies which have still not been coordinated between all of the sciences. The success of the Inter-Society Color Council in obtaining agreement between workers in all related sciences on a single terminology for color phenomena is an instance of the clearing up of the third type of difficulty. Fuller details of modern treatments of the problem are given by Ogden (2) and Seashore (3).

As might be expected from the continuity of subject matters among the sciences there is also a great deal of similarity in the nature of the problems studied in each field and likewise of the methods by which the problems are studied. Broadly speaking, most scientific problems fall under four classifications: (a) What are the basic descriptive units, e.g., electrons, cells, reflexes, into which the subject matter of any field may be analyzed, and what are the principal attributes or characteristics of these units, e.g., quality, amount or degree, time, and space; (b) what are the typical patterns in which these units occur, e.g., molecules, organs, adjustive reactions, and how are the previously mentioned attributes influenced by variations in patterns; (c) what are the quantitative relationships between any two units, attributes, or patterns; and (d) how do these phenomena develop?

The first three problems are answered by cross sectional or "static" methods, (a) and (b) being qualitative and (c) quantitative analyses, while a series of repetitions or a continuation of these same "static" methods over a longer period of time constitutes a developmental or "dynamic" study.

The old problem of the supposed difference between subjective and objective methods which was said to distinguish psychology from other sciences is no longer a problem. Objectivity is simply verifiability, as judged by descriptions of equivalent samples of a given phenomenon, and even the alleged "privacy of conscious-

ness" is no great difficulty. Science is interested in both the similarities and the differences between samples of a phenomenon to be studied. In biology and the social sciences we expect the variations to be larger from one sample to another than in the physical sciences for two reasons: (a) as a by product of greater complexity of the organizations studied, and (b) as a function of the lower stability of means or central tendencies in the small-samples studied in the life sciences, for example, ten to one hundred individuals as compared to the enormous samples studied in physical sciences, (millions of electrons, atoms, or molecules in samples such as those of the chemical element iron). But variability is a fact of considerable scientific importance in itself, and not a mere source of error or unreliability in measurements of central tendencies from one sample to the next.

Another problem which caused confusion until recently in psychology was the relative emphasis to be given to "atomistic" as compared to "organismic" analyses of psychological processes. It should be apparent from our previously mentioned classification of scientific problems that atomistic analyses are type (a) problems, while organismic or configurational analyses represent type (b). Both types are important and necessary to a complete scientific study of any subject matter. The four types of problems do not ordinarily progress at the same rate in any science, so that we may expect rather large shifts in interest or emphasis from one type of problem to another at successive stages in the advancement of scientific knowledge.

A further complication in the atomistic-organismic controversy is the failure to recognize the variations in observations which arise in shifting from macroscopic to microscopic methods of analysis. Thus a macroscopic analysis of an animal tissue may present an apparently continuous surface, whereas microscopic analysis may reveal discrete cell structures. In the same way ordinary analysis of perceptual phenomena may reveal only a "figure-ground" pattern, whereas a more refined analysis may reveal a much more minute pattern of continuously varying or discrete components. The term "fundamental descriptive unit" which is the basic interest in type (a) problems might imply either continuously variable or discrete phenomena.

An example of the way in which this type of controversy is being solved is given by the studies of Windle (4) which analyze the

earliest stages in the development of overt behavior in experimentally delivered fetuses of different species. Ordinary macroscopic observations by early investigators revealed complex movements which were interpreted as being unified from the very inception rather than arising from the combination of separate "atomistic" reflexes. Windle's later studies showed, however, that a large part of the "wide spread" nature of movements observed was due to the fact that such premature fetuses often become asphyxiated within thirty to sixty seconds of delivery because of inability to shift from the maternal blood supply to an external aerial supply of oxygen.

When observations were made during the first few seconds before asphyxiation could take place, isolated responses to stimuli were more characteristic. In a related series of studies reported by Carmichael (5) and others it was further shown that the intensity of the stimulus applied to a fetus was another factor which helped to determine whether the earliest response would be a relatively isolated movement of a single musculature or would irradiate to adjoining musculatures. Failure to control such factors as change from an embryonic liquid environment which helped to support body weight to an aerial environment in which the animal could not easily move limbs underneath its body also influenced the nature of responses elicited. The changes in the temperature of the maternal to the external environment were also suspected as sources of error in the older studies.

Though the old controversy between vitalistic and mechanistic viewpoints has largely disappeared from biology and psychology, the matter is in need of some clarification to avoid unnecessary arguments in the future. Although few if any scientists any longer hold that there is some "élan vital" or other nonphysical "vital force" which distinguishes living from nonliving phenomena, there is unfortunately some misunderstanding as to the exact nature of the modern "mechanistic" hypothesis. Thus while psychologists favoring the Gestalt viewpoint may not advocate a vitalistic hypothesis as to the nature of living organisms, yet nevertheless they may seriously criticize the "mechanistic" viewpoints which they attribute to the behavioristic and other theories.

In this case the assumption to which they really object appears to be the implication that animals, and especially human beings, behave like simple machines. This however is an unnecessarily



simplified interpretation of the mechanistic viewpoint. The selective responses of human sense organs are, in fact, often similar to those of various specialized physical instruments, e.g., the eye and photoelectric cells, the ear and microphones; in some cases the physical instruments are much more sensitive and cover a wider range of stimuli than the living organs. Likewise, the modes of response of the nervous system resemble in many ways a telegraphic system, each system having certain advantages and limitations. Much the same could be said of the effector systems in that physical machines may respond faster, more strongly, or with greater precision than living organisms.

Many of the objectors to a "mechanistic" viewpoint are not aware of the fact that modern physical, chemical, and electrical instruments can actually duplicate most of the separate functions of human organs, and even where this is known, critics often fail to consider that the mechanistic analogy of a human being with a machine would have to be a very complex machine having stimulus controls for light waves, sound waves, temperature, etc., and likewise with very complex amplifying, switching, or connecting and effecting systems, each of which systems may actually have been built as a separate unit, but not combined into a complete mechanical "robot" unit which could perform all or most human functions. The great forte of the human organism is its adaptability to many different functions.

Many scientists are also unaware that such phenomena as learning have been paralleled mechanically, as when an electrically controlled roller skate can be made to go through a maze once and thereby set a series of stepping switches so that on subsequent trips no errors will occur. Similarly, very few persons know that it is possible to state deductive problems of logic in a standardized symbolic fashion such that any syllogism can be entered on a key board of a specially built electrical switch box so designed as to indicate by flashing lamps whether the relationship is in accordance with accepted laws of inference, and if not, which type of logical fallacy is involved. Such actual demonstrations of human operations which can be paralleled by physical instruments, together with biochemical and biophysical studies of phenomena such as viruses which grade into nonliving chemical phenomena, appear to be gradually removing the older objections to a broadly interpreted "mechanistic" viewpoint in science.

BIOLOGICAL DETERMINANTS OF INDIVIDUAL DIFFERENCES  
IN HUMAN ABILITIES

In much the same way that we have tried to indicate the general assumptions and interpretive trends as to the biological nature of psychophysical functions, we may next proceed to summarize a large number of lines of evidence from recent research on the biological factors underlying individual differences in human performances. In accordance with our previous statements as to the continuity of knowledge between the sciences we may expect to find that a great deal of our information on this point comes from sources outside physiological psychology proper. Nevertheless it is important to construct an overall picture as to the way in which individual human beings function in producing the very large differences in effectiveness of performance in all psychological processes.

Probably the most striking fact about the importance of individual differences is that they are found in every activity so far measured, with a ratio of variation from lowest to highest of at least two to one, oftener five or ten to one, and sometimes over a hundred to one in effectiveness. Moreover these differences are usually found to be quite stable over any period of a few days, months, or years, which has immediately suggested to many persons that they must have an origin in biological inheritance. Rather than to state issues and weigh evidence in controversial fashion, which would go far beyond the scope of this article, the writer will here state a set of working hypotheses which seem to him adequate to correlate the present major lines of evidence.

(i) The findings that such anatomical factors as eye color, and various body structures seem to be inherited in accordance with Mendelian laws through genes in chromosomes suggest that there are probably inherited variations in each receptor, connector, and effector which go to make up the intact human organism.

(ii) Such inherited variations in biological structures would probably bring about corresponding variations in the effectiveness of performance by the intact organism in each type of activity in which the particular organs are involved. This however would not necessarily be true unless the individual had received an amount of motivation and training sufficient to approach the physiological limits of a critical organ, as will be outlined in a subsequent paragraph on the concept of biological capacity.

(iii) The correlation between individual variations in structure and variations in performance also implies that individual differences in abilities result largely from faster, stronger, or more precise reactions of the same kind. To the extent that individuals can also vary the nature of the work methods by which they accomplish the same general end results, this may not be true, since a handicap in one organ may be overcome by changing to a different work method in which the function of the deficient organ is not crucial.

(iv) Learning, or the development of an ability to execute a given type of performance, consists primarily in two types of change: (a) experimenting with various work methods until one is found that at least accomplishes the general result desired, however ineffectively, and (b) simplifying the successful method so as to drop out errors and irrelevant actions until only the essential steps remain, and then overlapping these remaining steps in time so that each step is anticipated as to its timing rather than waiting until the preceding step is completely finished, as in the case of branch assembly lines leading into the main assembly line of a modern factory.

(v) Many different work methods are possible for most complex practical performances, and variations in the effectiveness of these various kinds of methods are probably at least as important as the speed, strength, or precision with which any single method may be performed.

(vi) The same general kinds of qualitative and quantitative variation in work methods which are found in manual skills by engineering experts in time and motion study may be recognized in all human abilities, including sensory discriminations, affective reactions, and thought processes.

(vii) Usually these work methods are only slightly understood even by expert performers, since they have often been merely "hit upon" rather than having been developed as a result of detailed training instructions from expert coaches. In fact, even the most expert performers may be almost totally unable to explain how they do a thing or to teach this skill to another person.

(viii) Individual differences remain stable largely because we do so little to diagnose the particular factors in work methods which constitute "bottlenecks" in an individual's learning progress. Formal schooling consists largely in setting goals, demonstrating

rather than explaining methods, and relying on the individual's own self-diagnosis during practice to discover errors and suggest better methods. Methods also become habitual and difficult to change because they conflict with newer methods.

(ix) The use of machines, tools, and improved working conditions often serves much the same purpose as improving work methods, and most difficult human performances aside from (and perhaps even including) creative intellectual functions can be greatly facilitated by the use of these aids. In fact, it can be considered that, if any large scale production performance calls for continued human performance near the limits of capacity, the problem should be turned over to engineers and other experts for the provision of mechanical or other aids which will make such unusual effort unnecessary in any sustained work program.

(x) Very few of the typical evidences offered in behalf of a hereditarian hypothesis for the origin of individual differences in abilities are at all crucial to the problem. Thus the Kallikak and other early genealogical studies of the inheritance of mental deficiency involved not only differences in the intelligence of the parents but more or less parallel differences in the environments of each. The less intelligent parent came from a poor environment and successive generations of her offspring were also raised under these conditions: a crucial test would demand that they be placed in better environments to see whether this would make any difference. Likewise, the more intelligent parent came from better environments and was able to supply these advantages to her offspring, but the children were not tested by seeing if they would develop just the same even if placed in poorer environments. So far as these results go, either heredity or environment could have been the most important factor.

(xi) Early studies often suffered from the fact that many doctors did not know of the distinction between fraternal and identical twins, or at least left no record of the obstetrical facts which could alone be crucial as to their later classification in studies of twin resemblance. Retroactive classification of fraternal and identical twins according to degree of resemblance at later stages of development involves the dangers of circular reasoning, and begs the question. The accumulation of present day records of obstetrical classification of the two types should however make this method of co-twin control more useful, particularly where an experimenter can

control the different environments of each twin with respect to opportunities for developing a given type of behavior, as in the studies by McGraw (6).

(xii) It should be recognized that most of our present data on the effects of changing environments of children has come from changes which were made for ordinary purposes, such as finding a foster home, and not for the deliberate purpose of providing ideal experimental environments. Often, too, the change in environment was not great, but merely from one part of the middle range to an adjacent level of desirability. The only relatively clear cut data come from three series of studies which are unfortunately still little known to many people either in or out of psychology. The study of Skodak (7) shows that fifteen foster children whose true mothers were definitely feeble-minded and whose fathers were predominantly from the lower economic levels, when placed before the age of six months in average and superior foster homes exhibited almost exactly the same average intelligence quotients as those of true children of such parents. Their average intelligence quotients were 116, 111, and 111 at the average ages of two, four, and six years respectively. This is definitely contrary to a hypothesis emphasizing the importance of hereditary factors, and is in accordance with environmental hypotheses, as outlined by Wellman (8).

Speer (9) studied sixty-eight children who were tested for intelligence when they were taken from mothers who were committed to Illinois institutions for the feeble-minded. The test scores showed a definite decline in intelligence in proportion to the number of years they had lived with their feeble-minded parent. Children below the age of two averaged 100.5 in intelligence quotient, with none feeble-minded (none were below 90), while the children twelve or older in chronological age averaged 53.1 with none in the normal range above 70.

The study of Skeels *et al.* (10) on the small but cumulative effects of preschool experience in increasing intelligence had its counterpart in an orphanage study in which the subjects showed gradual decreases in measured intelligence, which levels were raised however in the cases of children given preschool advantages.

A recent study by Lorge (11) reports a follow-up series of tests comparing 131 New York boys who were equal in intelligence at the end of the eighth grade (average age 14) but who differed in their subsequent histories in that half went on through high school

and college while the other half stopped their formal education and went to work. Twenty years later, the group of boys who had completed college averaged 15 points higher in intelligence quotient, while the control or noncollege group, originally equal in this ability, remained at the same level as when they left the eighth grade. Clearly this represents a marked environmental effect.

Schmidt has shown in a further study (12) of the cumulative effects of an elementary vocational school curriculum for children who had been classified by psychological tests as feeble-minded and unable to profit from regular city schools, that a program of teaching designed to meet the everyday needs of the individual children enabled them to show even more marked gains in intelligence, educational progress, vocational success, and personal adjustment. Additional data are already available as to the fuller effects of this experiment, together with comparable data from a similar group of children given the more traditional type of vocational (largely manual) training.

By way of summary thus far, let us examine a set of definitions of the basic terms, *skills*, *abilities*, *aptitudes*, and *capacities* to see more clearly the probable role of biological factors as determinants of individual differences in various functional characteristics.<sup>1</sup>

(i) *Skill*.—A person's skill in a given performance is his present effectiveness in terms of end results, e.g., speed, precision, strength, a qualitative characteristic (such as rhythm), or a combination thereof. It is further connoted that this degree of skill is dependent upon the particular work method employed, including the extent of overlapping in the timing component actions. It may also be connoted that of two persons attaining the same end results, the one who does so at a lower energy cost is said to be more skillful.

(ii) *Ability*.—What one is able to do in a given performance at a given time. Synonymous with present skills, but often misused in the sense of ultimate capacity.

(iii) *Aptitude*.—An individual's aptitude for a given performance is his probable rate, or possible ease, of learning a skill, or both, as estimated from sample related factors, e.g., (a) favorable structures or physical functional constants of organs; (b) transfer of training as shown in adoption of favorable work methods—general methods of approach to a problem for developing new methods from previous similar activities. It is further connoted that: (c) such aptitudes are ordinarily quite stable, but may change as a result of intensive training; (d) rapidity of learning is positively correlated with high ultimate capacity (?); (e) high aptitude leads to ease in terms of low energy cost per unit of output; (f) interest and satisfaction in the exercise of potential ability is easily developed; (g) aptitudes are

<sup>1</sup> These definitions by the writer and A. C. Van Dusen were published in condensed form by Jones & Seashore (13). The background of the concept of work methods underlying all abilities is given in an earlier work by Seashore (14).

relatively specific, or at most, are related only within small groups.

(iv) *Capacity*.—A person's functional capacity for a given performance or skill is his maximal, potential effectiveness in terms of end results (i.e., speed, precision, strength, qualitative characteristic, or a combination thereof), which may be achieved by using a given work method with maximal overlapping of component actions, after optimal training. It is further connoted that: (a) the functional limit is based in turn on anatomical and physiological constants of separate organs involved in the given work method and on their integration through neural and humoral systems; (b) conversely, change to a work method involving a different set of organs would result in a different capacity; (c) a change in work methods alone, utilizing the same organs, could still change the capacity; (d) the capacity is relatively stable for each work method, this being usually attributed in large part to inheritance of the anatomical and physiological characteristics which are involved; (e) while minor variations arise due to differences in age, health, and motivation, the individual tends to retain his relative ranking among others subjected to the same working conditions; (f) optimal training includes both direct and transferred training under expert supervision; (g) adequate tools, materials, and working conditions are assumed; (h) since capacity refers to a potential limit, it can only be inferred. This could only be done by extrapolation of an individual's performance at any stage of his learning curve for a particular skill, on the assumption that he will develop further in about the same way that others have done who showed the same initial rate of progress. These learning curves are probably asymptotic to a hypothetical ultimate level; and (i) initial rate of progress is thereby assumed to be significantly and positively correlated with ultimate capacity in any performance in which practice produces a significant amount of improvement, and in which the units of measurement are sufficiently fine to discriminate actual differences in effectiveness at the more difficult stages of performance.

The term capacity does not represent a very useful concept, since a person's capacity in a given skill can only be inferred, and is not operationally defined so that it could be readily observed. In most cases the concept of aptitude is more useful.

It may be mentioned in passing that scores in general intelligence tests are simply the sum of points earned in a sample of various types of overlapping verbal skills in problem solving, each one of which is definitely subject to improvement by training. An intelligence test simply determines about how far a person has risen in his mastery of such a sample of common skills, and is important partly because these skills are often prerequisite to, or at least a head start in, acquiring other more complex practical skills.

Perhaps the clearest evidence of the importance of individualized training in developing an important human ability is the study of Wyatt (15) on the improvability of pitch discrimination. The subjects were eight students selected by the faculty of a university school of music as the most persistently in error in pitch intonation, plus a comparison group of eight nonmusic students selected by their extremely poor scores on the Seashore phonograph test of



pitch discrimination. Initial thresholds were first carefully measured by individual testing on automatically controlled tunable bars, on a phonograph, and on an audio-oscillator at three different pitch levels. Following this, about eight hours of diagnostic remedial training designed to meet the particular needs of each student were given on one oscillator frequency, with supplementary training on the Conn chromatic stroboscope which visualizes small errors in pitch intonation. At the end of this time the retests on the same instruments showed that all but three of the subjects were now above average for their respective groups of musicians and nonmusicians, and some were near the top of their groups on the particular frequency used in training. They also showed marked transfer of training to the slightly different tone qualities of the tunable bars and phonograph records, as well as moderate transfer to higher and lower frequencies on the audio-oscillator. Introspective comments of the subjects further support the hypothesis that qualitative variations in work methods underlay much of the initial difficulties as well as later improvements in quantitative thresholds. Evidently auditory discrimination thresholds are markedly subject to improvement by specialized training even though ordinary musical training is likely to be relatively ineffective.

In a somewhat parallel fashion individual differences in degree of emotional adjustment are often analyzable into underlying qualitative differences in the problem solving methods or mechanisms employed in meeting conflict situations. Here we find that not only does a strong emotion influence the type of behavior (or work method) employed in a situation but also that the relative effectiveness of the particular mechanism adopted has a good deal to do with decreasing or augmenting the emotion from which it arose. It is a sort of "chicken and egg" cycle in which it is difficult to say in which direction the influence is more important. The great difficulty which has always been encountered in attempting to classify mental disorders (extreme emotional maladjustments) may be better understood if we consider that the various symptoms represent the use of different mental mechanisms (overcompensation, repression, regression, etc.) which people adopt and which are by no means mutually exclusive methods of problem solving. Since the mechanisms are partially equivalent methods of problem solving, usually employed in combination, it is no wonder that we find a continuous variation of patterns of maladjustment rather than a limited number of clear cut syndromes. The concept

of mental mechanisms as problem solving methods of widely varying effectiveness also helps us to understand why there can be functional mental disorders with no known organic basis in the sense of a focal infection or physical trauma to an organ.

As shown by Seashore & Katz (16) a person's temperament may be described in terms of his habitual methods of responding to conflict situations and these methods may be evaluated quantitatively as to the extent to which they satisfy three criteria: (a) attaining the original goal or a genuinely desirable substitute; (b) attaining or maintaining social approval in so doing; and (c) the value or cost to other persons of the method adopted in satisfying the individual's own needs.

In the area of motor skills we find probably the clearest experimental evidence for the importance of work methods in determining individual effectiveness of performance of a given function. Here the well known motion picture techniques of motion study engineers are available as routine engineering services in determining the most effective work methods for a given industrial operation, and in training workers to use these methods.

In a review of a long series of experimental and theoretical analyses of individual differences in fine manual skills the present writer (17) cites the following lines of evidence as indicating the importance of work methods rather than biological variations in component receptors, connectors, and effectors in determining a person's ability in a given type of performance:<sup>2</sup> (a) Shifting from one musculature to another, e.g., from right to left hand, or from hand to foot, has very little effect in determining a person's rank in a group with respect to any relatively simple performance such as simple or serial reaction time, rate of tapping, rhythmic coordination, etc.; (b) changing the cues or signals for a performance (e.g., reaction time) from one sense field to another (e.g., vision to audition) ordinarily makes only moderate differences in group rankings as to skill, indicating that sensory factors are of some significance as determinants of motor abilities; and (c) even keeping the musculature and sense field constant (response of right hand to visual cues), if the pattern of the action is varied significantly, by changing from simple reaction to tapping tests, the changes in ranks from one test to another will usually be quite large, indicat-

<sup>2</sup> Hereditary differences in structural characteristics are large and important between species, but are apparently much less important than we have previously thought between members of the same species.

ing that the pattern of the performance is the most significant factor underlying individual differences in fine motor skills.

Gross motor coordinations of an athletic nature are not significantly correlated with abilities in fine manual coordinations, such as reaction time, tapping, or pursuit (continuous coordination) tests. Neither are scores on fine manual tests at all closely correlated with each other except within relatively narrow group factors. Neither are these measures of fine motor speed or precision at all closely related to competence in mechanical abilities, where "know how," "tricks of the trade," and special tools and materials are usually of far greater importance than speed, strength, or steadiness of hand.

#### EFFECTS OF EXTREME WORKING CONDITIONS UPON EFFECTIVENESS OF PERFORMANCE

One of the first generalizations which one may draw from the numerous experiments upon extreme working conditions is that human mechanisms are so adaptable to a variety of conditions that aside from short periods of adaptation most measures of effectiveness in psychological performances show little or no decrement from more normal situations. Even where an occasional measure shows a statistically significant difference between the normal and extreme working conditions it is often so small as to be of little practical importance. Thus a variety of experiments upon high temperatures, high and low humidities, low barometric pressures as in altitude studies, and high levels of distracting stimuli show that contrary to our expectations in everyday life, these extreme conditions need not produce any marked decrement in performance until the situation becomes very unusual. In everyday life extreme conditions of temperature, etc., do usually produce decrements, but under experimental conditions of the laboratory they do not. How then may we account for these discrepancies?

If we except measures of gross bodily strength such as athletic performances, in which significant decrements can be produced within a few seconds or minutes, it appears that most practical performances do not demand that an individual should approach a physiological limit of any organ for more than a moment or two at a time, and that even after prolonged activity one may recover temporarily for a few moments to approach the best performance made under optimal conditions. For this reason measures of intermittent activity, such as reaction time, in which one may relax

between trials, are usually rather insensitive to types of change which might be expected to produce considerable decrement, such as fatigue.

The next explanation which suggests itself for the difference between everyday decrements in performance and the lack of decrements under laboratory experimental conditions is that a great deal of so-called fatigue is merely boredom or negative adaptation to certain types of stimulation. Additional motivation (background stimulation) can be added to overcome the raised sensory and motor thresholds, or different motivation may activate organs which have not yet become negatively adapted. In everyday life if we are tired or distracted we can give up by shifting easily from one activity to another, or by relaxing our efforts in general; but in the laboratory situation the experimental motivation is always to see what we can do if we have to. Thus, in an unpublished study by the writer, students who were given comparable reading tasks under conditions of playing for forty minutes out-of-date popular phonograph records did no worse on objective tests of comprehension than under the control conditions of normal quiet. In everyday life they might easily have been partially distracted or might have given up studying if desired, but under the experimental conditions the instructions were to persist in spite of the distractions. Apparently the challenge of the experimental situation is a major source of additional stimulation which approximately balances out any other factors which may cause actual interference with any phase of the normal reading process.

According to the foregoing interpretation one might expect that the maintenance of normal effectiveness under extreme working conditions would involve a greater expenditure of energy than under normal conditions. This was in fact shown by an early study of Laird (18) on the relative metabolic rates of typists working under office conditions of high noise level from a busy street as compared to the same office after the noise level had been reduced by acoustical materials. In the case of a sedentary occupation such as typing the extra metabolic cost may not be large enough to produce a significant amount of genuine muscular fatigue, but in other more active occupations the decrement might become large enough to cause discomfort and fatigue.

If the principal effects of extreme working conditions are largely to produce negative adaptation or raised thresholds of various organs, other stimulation can be added to activate these same

organs or other organs which may be employed in an equivalent work method. Attending to substitute cues should therefore be an important method of overcoming normal decrements in performance. From this we might expect that continuous complex performances calling for more or less simultaneous attention to several different sets of cues might be the most sensitive measures of the effect of extreme working conditions upon an individual's performance. Such continuous and complex performances should present many more chances of catching the person off guard with respect to any single slight cues for which the thresholds may have been raised, and any attempts to shift to other cues may interfere with other aspects of the complex process.

It is interesting to note that in the largest series of experiments of attempting to predict success in practical motor skills, namely the Army Air Force psychomotor tests for selecting flyers, the tests of least predictive value were those of simpler reaction time and hand steadiness, both involving short trials on simple performances, while the tests of greatest value were those of continuous coordination at high speed, some of which had no apparent resemblance to the normal motions of operating an aeroplane. This raises the question of whether or not there may be a general factor of ability to organize one's efforts in such a way as to overcome confusion in a variety of complex types of coordinations. This may of course be tested by introducing a variety of complex tests which do not emphasize precision in manual control to see if they are or are not correlated with the complex psychomotor test scores.

In cases where there is an immediate decrement in effectiveness following a large change in working conditions, as in shifting from one climate to another, there is often a gradual adaptation to the new conditions. An interesting and valuable series of studies on acclimatization to the effects of high temperatures, with low humidities as in desert conditions, has recently been reported by Bean & Eichna (19). It is difficult to improve upon their own concise summaries as to the significant factors underlying rate of acclimatization, as follows:

1. Performance in hot environments depends greatly on the state of acclimatization.
2. A man acclimatized to heat works in the heat with a lower body temperature, lower heart rate and a more stable blood pressure, than when not acclimatized. Nevertheless, acclimatization to heat cannot be measured by these criteria alone, as they do not necessarily correlate with the man's behavior and ability to work. The man as a whole must be considered and evaluated.

3. Acclimatization to heat begins with the first exposure, progresses rapidly and is well developed by the third or fourth day.

4. Subjects in good physical condition acclimatize more quickly and are capable of a greater work output in the heat than are men in poor physical condition.

5. Continued training in cool environments beyond that necessary to attain good physical fitness does not further increase the ability to work in the heat nor shorten the period of acclimatization.

6. Resting for three or four days in the heat, with activity limited to that required for subsistence, results in definite, but only partial acclimatization. Some work in the heat is necessary for complete acclimatization.

7. Full acclimatization (the ability to perform a maximum amount of strenuous work in the heat) is attained most quickly by graded, progressively increasing work in the heat.

8. Strenuous work on first exposure to the heat is not well tolerated and will often result in disability. If such work is maintained for several days many men will become incapacitated and those who continue to work do so ineffectively and inefficiently.

9. Intolerance to heat on first exposure, even to the point of heat exhaustion, does not retard the rate of acclimatization or lessen the degree which is finally attained, *provided* work is discontinued when symptoms appear, water and salt are given, and subsequent work is within the capacity of the subject.

10. Three or four exposures to heat of 3 and 4 hours duration with two one-hour work periods during each exposure, will produce a considerable degree of acclimatization. These exposures may be separated by intervals of two days in a cool environment.

11. The pattern of acclimatization is the same for short severe exertion as for moderate work of long duration.

12. Inadequate rest at night results in less work or less efficient work on the ensuing day, even by the well acclimatized man.

13. Acclimatization is well retained for one to two weeks, after which it is lost at a variable rate. Most men lose the major portion of their acclimatization in one month—a few are able to retain it for two months. Men who remain in good physical condition retain their acclimatization best. Repeated exposures to heat are required at intervals not exceeding one month, if a high degree of acclimatization is to be maintained for long periods of time.

14. The amount of work accomplished on first exposure to heat can be increased by drinking water in amounts equal to the weight (sweat) lost during work. The rate and final degree of acclimatization attained are not influenced by the water intake (forced, moderately restricted, or taken as desired) during the first two or three days of work in the heat, *provided* that after this initial period men are permitted as much water as desired.

15. Suddenly restricting the water intake of men working in the heat leads to a deterioration of morale and motivation, reduces greatly the efficiency with which work is performed, decreases the total work output and causes disabling symptoms in many men. This holds for even the well-acclimatized man. Gradual reduction of water intake induces changes similar to sudden restriction, differing only in that they are produced more slowly.

16. Acclimatization to hot dry (desert) environments increases markedly the ability of men to work efficiently and effectively in hot moist (jungle) environments.

In a parallel study of hot and humid conditions Eichna, Bean, Ashe & Nelson (20) have again summarized very adequately the process of acclimatization to the effects of tropical climates.

Men adapt themselves to work in humid heat by a process of acclimatization which enables them to work more efficiently and with less risk of illness than when first exposed. The acclimatized man works with lower heart rate, lower skin and rectal temperature, more stable blood pressure and less discomfort than when unacclimatized. Acclimatization to heat begins with the first exposure, is achieved most rapidly and completely by progressively increased work in the heat, and is complete in 7 to 10 days. Resting in humid heat induces but little acclimatization. Physically fit men acclimatize more rapidly than unfit men and when acclimatized are capable of more efficient work. Acclimatization develops most rapidly when the original environment is warm (summer) and is retained longest when the return is into a warm climate. Strenuous work on first exposure to humid heat is not well tolerated and leads to disability which, however, need not retard nor decrease the final acclimatization attained, *provided* rest, water and salt are supplied. There is a measure of cross acclimatization between hot-dry and hot-humid environments.

The performance of acclimatized men in humid heat is impaired most seriously by lack of adequate water intake and lack of physical fitness. It is also affected adversely, but not so severely, by lack of rest and sleep, by added clothing and equipment, alcohol and long periods of work.

Sweating in humid heat is profuse, grossly inefficient, wastes water and salt and is independent of the fluid intake. Replacement of the lost water and salt is essential to efficient performance. Thirst is a lagging guide to these needs.

In evaluating these studies of what man can do under extreme conditions we should not stress too heavily the fact that one can perform almost as well as under more normal conditions. If it is true that this is done at a higher cost in energy, these results may be cumulative and show up in practical situations which continue over a longer period of time than those of most experiments. Furthermore, we as psychologists should be equally concerned with the feelings of workers, whether they can enjoy or can only tolerate conditions, particularly when these conditions can be improved by present known methods as feasible as air conditioning. It is equally important to know how people can compensate so as to maintain normal effectiveness under emergency conditions, and to avoid abusing this possibility of unduly strenuous types of effort when more normal conditions of peacetime life make it unnecessary. For the long view of practical performances in everyday life we should always seek a work method which is easily within the range of most person's capabilities, overcoming the most difficult aspects of the performance by instruction in superior work methods or by supplying superior machines, tools, or working condi-



tions. Often the most intelligent action is to adapt the situation to the individual rather than to select or adapt the individual for the situation as we are likely to try on first thought or in emergencies such as those of military necessity.

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## APPLIED PHYSIOLOGY\*

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This review will emphasize the physical well-being of active men exposed to stresses of work, environment, diet, drugs, and toxic agents. The position will be taken that an important function of applied physiology is to demonstrate ways of improving performance and of preventing deterioration under stress. The general fields of industrial medicine and the physiology of low and high barometric pressures will not be discussed except when they occasionally provide pertinent examples illustrating important points. Necessary restrictions on the mention of confidential material make discussion less complete and timely than one would desire.

### PHYSICAL FITNESS

Programs of physical training were developed during the war to an unprecedented extent not only in the armed forces but also in schools and colleges. Two reasons for this were that, in spite of mechanization, some men, especially in the ground forces, were daily called upon to put forth a large amount of physical exertion; and that in perilous situations any man's existence may depend upon his physical stamina. In the background was also the feeling that improvement in physical fitness is, at the same time, an aid to efficiency in activities not necessarily requiring much physical exertion, such as piloting aircraft or working in a hospital. This tenet, widespread since Homeric times, has never been systematically studied nor convincingly proved. Perhaps it will be possible to obtain evidence by study of the records kept by some services of the performance in actual combat of large numbers of men who had during training been subjected to rigorous programs of physical training and to periodic tests of fitness.

Quantitative assessment of physical fitness is one of the most complex and controversial problems in applied physiology. This situation arises in part from lack of general agreement on what constitutes fitness for withstanding various types of stress, and in part from lack of agreement on what measurements allow valid

\* This review covers the period from September 1942 to August 1945.

comparisons to be made among different individuals exposed to the same stress. The discussion in the remainder of this section will be limited to physical stamina.

Two fundamental hypotheses are implicit or explicit in most of the papers in this field. First is the concept that there are quantitatively measurable differences between the fit and the unfit. Second is the hypothesis that a distinction can be made between fundamental physiological adaptations common to fitness for all types of exertion and the special skills necessary for the successful performance of different types of physical endeavor. Physiological measurements proposed by various observers for testing fitness have been chosen after consideration of the course of events during exercise and the changes that can be measured in a subject during a course of training (1).

Physical exertion disturbs the homeostatic equilibria of the resting state and the more violent the exercise the further are these equilibria displaced. Work can be carried on in a steady state if new equilibria can be maintained, but if they cannot be achieved the subject has to stop sooner or later from exhaustion or else slow down to a pace at which he can establish new equilibria. A distinction has therefore been drawn customarily and rightly between moderate and exhausting work. If unquestionably fit and unfit men of the same height and weight are compared while performing the same work which both can sustain in a steady state, the fit man shows: lower oxygen consumption (2); slower pulse rate during work (2); lower systolic blood pressure during work (2); larger stroke volume (2); lower blood lactate during work (3); and faster return of blood pressure and pulse rate to resting value after work (2). If both are performing the same work which neither can sustain in a steady state, the fit man shows: longer duration of effort before exhaustion (4); higher oxygen consumption (3); somewhat slower maximal pulse rate (4); larger stroke volume (3); higher blood lactate (4); and faster return of blood pressure to normal after work (4). To generalize, the fit man carries on a given grade of moderate work with less displacement of his physiological equilibria. He can establish steady states at higher grades of work. If forced he can displace his physiological equilibria further and for a longer time. Finally, he has better recuperative powers in the sense that after a bout of exhausting exercise he returns to his normal resting state more quickly.

There can be little disagreement that certain groups of athletes, such as oarsmen and long distance runners, are good examples of men fit for long sustained exertion. Likewise, groups of men taken at random provide a wide variety of subjects ranging from the very unfit to those almost as fit as athletes in training. Physiological measurements suitable for assessing fitness can be selected from those showing significant differences between the above two groups. Such measurements should satisfy at least two important requirements (5): First, they should show group differences between men in good training and men not in good training, including the same individuals in and out of training. Second, even when group differences can be demonstrated, measurements are not suitable if they make obvious errors in the case of even a few individuals. The various physiological mechanisms involved in muscular exercise are so closely interrelated that in the case of individual subjects who have been studied intensively, if rate and duration of work are known and a measurement is made of one of the variables cardiac output, pulmonary ventilation, oxygen consumption, carbon dioxide output, blood lactate, oxygen debt, blood pressure, and pulse rate during and after exercise, then fairly accurate estimates can be made of the values of the other measurements (5). Nevertheless, when judged by the criteria described above not all measurements at all grades of work are satisfactory for comparing one individual with another. Measurements made during work which all subjects however unfit can carry out in a steady state are of little help in comparative assessment, mainly because the differences between the fit and the unfit are arithmetically smaller and less regular the lower the metabolic rate. Measurements on the resting subject have been criticized by some observers for this reason, especially the resting pulse rate and blood pressure (6).

Tests of physical fitness now widely used have in common the imposition of exercises that put the cardiovascular system under considerable stress by involving large muscle groups at fairly high grades of work without demanding unusual types of skill (5, 7 to 11). Emphasis is usually placed on actual performance as measured by duration or amount of work performed at a fixed pace and on physiological measurements which relate to cardiovascular efficiency, such as oxygen consumption, pulse rate, blood pressure, and blood lactate. For practical purposes most of these measurements cannot be made readily in the field so that pulse rate during

or after exercise is the most widely used physiological measurement.

Systematic reviews on physical fitness tests have been presented by C. Taylor (12) and by H. L. Taylor & Brozek (13). A generalization repeatedly emphasized by those who apply tests is that successful performance depends upon at least three essential factors: anatomical normality, functional integrity, and motivation to do well. In all acceptable tests now in use poor scores will be made by subjects in whom any one of these three factors is low. The ideal test would eliminate the psychological factor. However, it is unlikely that any such test can be devised for the reason outlined above that consistent physiological differences between the fit and the unfit are measurable only when the subjects undergo stress and the more severe the stress the more apparent the differences become (5).

One of the most satisfactory applications of tests of physical fitness is when the same individual has to be compared with himself from time to time to detect alterations in his physical condition. Examples are to be found in numerous papers in the field of nutrition where studies have been made of the effects for good or ill of changing caloric intake (14), and of subjecting men to a plethora or deficiency of various vitamins such as thiamine (15, 16) and ascorbic acid (17). Another such application is in following the results of programs of physical training. With the aid of suitable tests administered periodically it is possible to determine whether the optimal amount of training is being given, to segregate subjects into classes so that the work will not be too hard for some and too easy for others, and to determine when a given subject has improved enough to be shifted to another class in which he will receive optimal training (18). Two conclusions of considerable practical importance are supported by such observations. First, it appears impossible at present to predict by a single examination how much a given subject is capable of improving with training. Second, men in reasonably good condition at the start of a program require a more vigorous program to improve significantly than do men in poor condition (18).

Clinical applications of tests of physical fitness have been made in programs of rehabilitation and convalescence. It is of course important to make objective and quantitative measurements of the physical condition of patients whose quick return to active life

is desired. Karpovich, Starr & Weiss (19) described a program at Randolph Field in which the primary objective was the quickest possible convalescence following acute febrile illnesses. Graded step tests were used for deciding what degree of activity should be allowed at different stages of recovery. Testing and participation in the physical training of the convalescent training program reduced hospitalization somewhat, definitely did not prolong illness, and insured adequate physical fitness for return to full military duty.

Another clinical application of physical fitness tests has been in the study of neurocirculatory asthenia. Jones & Scarisbrick (20) at the Mill Hill Emergency Hospital concluded that the syndrome is essentially a neurosis and that a majority of cases fit naturally into recognized psychiatric categories. Their physiological observations included exercise tolerance tests, respiratory exercise, tolerance tests, and measurements of the lactic acid, pH, and carbon dioxide content of arterialized venous blood during exercise on the bicycle ergometer. Their patients broke down in maximal effort with abnormally low lactic acid and abnormally high pH and carbon dioxide, and they concluded that there was no evidence of advanced physiological fatigue in such a situation. It is always difficult to decide whether different workers are studying the same type of psychiatric patients and so it is not surprising that the conclusions of the English workers were not fully supported by Cohn and associates at the Massachusetts General Hospital (21). Their patients had complained for many years of dizziness, palpitation, chest discomfort, and dyspnea. This had been associated with inability to do hard work, nervousness, and emotional instability. The patients were exposed to walking and running on a treadmill and physiological measurements included pulmonary ventilation, oxygen consumption, pulse rate during and after work, and blood lactate. Physical fitness was extremely poor. Maximal effort produced abnormally small displacements of homeostasis, and moderate work produced abnormally large displacements, a situation seen in men who are in poor physical condition. This suggests that their intolerance to effort was not caused solely by poor motivation, but was associated with true physiological fatigue. The complete genetic, psychiatric, and clinical studies of this same group of observers lend strong support to the view that these patients are congenitally inferior in many ways (22). A reasonable explanation for the

syndrome's predominance among military neuropsychiatric casualties is that many men, who in peacetime would have been able to choose a mode of life compatible with their inferiority, in wartime have to carry out tasks beyond their capacities no matter how good their training has been. They cannot succeed, their disability comes to the attention of their superiors, and eventually they are referred to the medical officer. Rheingold (23) has discussed constitutional pathological states and military fitness.

In the complex problem of comparing one man with another, tests of physical fitness have to be used with reservations. There is a widespread natural reluctance to accept their results as indicating anything more than a subject's capacity at a given time to perform a given arbitrarily assigned task. In some circumstances it would no doubt be desirable to select from a large group a smaller group ready for immediate arduous duty, but such preselection was not widely practiced in wartime. In general, men were required to meet certain minimal physical and mental standards, were trained, and were sent into active duty. Those who could not stand the pace at any stage were transferred, placed on limited duty, or given medical discharges. Such a process was possibly wasteful of money and manpower, but there is no clear evidence available that it would have been possible to obtain better results than were in fact obtained. It is doubtful that any satisfactory tests were available even for solving such relatively simple problems as preselecting men for duty in the desert, the moist tropics, the arctic regions, or the mountains. In the case of preselection of officer material a systematic, comprehensive, and ambitious program was presented by the Grant Study at Harvard University (24, 25, 26). The factual basis for this program was a long term study on college students. The fundamental conception was that officers should be in good bodily health, stable emotionally, of sound intellect, and physically fit. There can be little disagreement with these ideas, but there may be some question about the tests recommended, which were: (a) an eight minute test of physical fitness for measuring ability to withstand hard muscular work; (b) a ten minute interview devoted to the study of personality and activities; (c) a brief inspection of body build to determine characteristics of masculinity which are related to physical fitness and personality. This system was never adopted officially by any of the services but observations were made by the Grant Study on many candidates for commissions in the U. S. Army and Navy.



They reported good agreement between ratings arrived at by the methods of the Grant Study and by the usual methods of the Army and Navy. Enough men were examined to enable a valid study to be made correlating actual performance in the war with predictions made before entry into the service.

### HEAT

There is gratifying agreement among various research groups concerning the general conditions under which young men working in the heat reach their best performance, and Table I lists the most important requirements for both moist and dry heat. The discussion below will take up successively the three categories: general condition, heat balance, and nutrition.

TABLE I  
CONDITIONS FOR THE BEST PERFORMANCE OF YOUNG MEN WORKING  
IN THE HEAT

Condition	References
1. General	
<i>a.</i> No chronic or acute debilitating diseases	27, 28
<i>b.</i> Good general physical condition	29, 30, 31
2. Heat Balance	
<i>a.</i> Complete acclimatization for the particular environment and work encountered	29, 30, 31, 32, 33
<i>b.</i> Avoidance of unfavorable environmental conditions and excessive rates of work	34, 35, 36, 37
<i>c.</i> As little clothing as consistent with protection against radiation and trauma	31, 34, 38, 39
3. Nutrition	
<i>a.</i> Maintenance of complete hydration hour by hour	30, 31, 40, 41, 42, 43
<i>b.</i> Maintenance of adequate salt intake day by day	44, 45
<i>c.</i> Maintenance of adequate intake of carbohydrate, total calories, and water soluble vitamins	46

### GENERAL CONDITION

It is almost axiomatic that the same person will perform better in the heat when he is well than when, for instance, he is debilitated by malaria. When one talks of a healthy person without defining his physical condition as poor or good, there is some room for discussion. Nevertheless, most textbooks of tropical medicine recommend, and general experience in the tropics supports this recommendation, that white men take regular vigorous exercise (27). It

is a common laboratory experience to find that in a group of subjects the man who is fittest for long sustained work in a temperate environment is also fittest for long sustained work in the heat; and also that the same individual performs better in the hot room when he is in training than when he is not (30, 31).

#### HEAT BALANCE

*Acclimatization.*—Turning to factors directly related to heat balance, we shall discuss acclimatization, heat load, and clothing (Table I, 2). One of the most spectacular adaptations in normal human physiology is the rapid acclimatization which ensues when a man fully trained for a fixed task in a temperate environment is forced to perform the same fixed task repeatedly in a hot environment. In any treatment of acclimatization one must bear in mind three important considerations. First, even a fully acclimatized man can be thrown into a state of exhaustion indistinguishable from that of his first day if all the conditions listed in Table I are not met. Second, sharp distinction has to be made among rest, work at a rate that can be carried out in a steady state after acclimatization, and work at a pace which can never be carried out in a steady state no matter how good acclimatization may be. Third, there are large differences among men in tolerance to heat both before and after acclimatization. Certain features are well established. Comfort is greatly increased, duration of effort prolonged, and susceptibility to exhaustion decreased (29 to 33). Acclimatization to one set of conditions gives complete acclimatization for less severe but only partial for more severe conditions (29, 30), and acclimatization for a given dry environment provides only partial acclimatization for a moist environment of the same equivalent temperature (29, 30). One achieved, acclimatization persists for a considerable time after the last exposure to heat (29, 33). In rest and steady state work, rises in rectal and skin temperatures are minimized and the efficiency of sweating, i.e., the effective cooling power of a given amount of sweat, is greatly increased (29). In work which cannot be carried out in a steady state rectal and skin temperatures rise maximally, but the efficiency of sweating is still high. In rest and moderate work, rises in pulse rate are minimized, dependent edema is ameliorated, and orthostatic hypotension and malar flush no longer appear (29 to 33). In exhausting work manifestations of cardiovascular difficulty can be equally severe before

and after acclimatization (29, 35). In moderate work pulmonary ventilation and oxygen consumption are usually decreased (29). In rest and steady-state work, there is usually an increased rate of sweating (29 to 32) and in exhausting work there is a consistent marked increase in capacity to sweat (34, 35). Sweat chloride tends to decrease in rest and steady-state work, but in hard work there is no change (47). Some of the disagreements in the literature on sweat chloride during acclimatization have been in part reconciled by the finding that the levels of sweat chloride and sodium, but not potassium, are related to a central factor, measured by rectal temperature and rate of sweating, to a local factor measured by skin temperature, and to personal idiosyncrasy as measured by large differences between individuals even when rate of sweating, skin temperature, and rectal temperature are the same. Therefore one would expect sweat chloride to decrease during acclimatization for a fixed task in a fixed environment, because of the well recognized decreases in rectal and skin temperatures; but not to decrease in exhausting work when these remain high. These expectations were verified experimentally (47). No consistent changes have been observed in formed elements or constituents of the blood. No systematic studies have as yet been reported of biochemical balance, nervous, endocrine, digestive, or excretory systems. Any hypothesis on the mechanism of acclimatization must be rather unsatisfactory until the role of the endocrines and nervous system is elucidated. One hypothesis which fits most of the known facts concerns the vasomotor centers of the thalamohypothalamic regions. On first exposure to heat there is inefficient capillary circulation in the skin, with inefficient cooling of the blood and inefficient venous return from the skin. This might account for the great discomfort, increased rectal temperature, inefficient cooling power of a given volume of sweat, high skin temperature, malar flush, orthostatic hypotension, high pulse rate, and dependent edema. After the thalamic centers secure control over the skin capillary bed as a result of subsequent exposures to the heat, the above extreme displacements of homeostasis are minimized. Changes in respiratory functions may be explained on the basis of changes in body temperature.

The practical application of present knowledge of acclimatization is clear. Men exposed to an unaccustomed hot environment must become acclimatized before being asked to work to full ca-

capacity. This can be achieved best by their working on the first few days of exposure, but only moderately hard and with careful watch for signs of exhaustion.

*Equivalent temperatures.*—The concept of "equivalent temperature," where the cooling power of environments is the same even though dry bulb and wet bulb temperatures and wind velocity might all be different, has been extended by two mutually complementary pieces of research. The objectives of both were in the direction of defining "equivalence" in terms of quantitative physiological measurements, but the experimental approaches were radically different. The aim of Robinson and colleagues was to predict the average physiological stress of different environments (34). Fully acclimatized and fully hydrated subjects performed a fixed task at each exposure. The overall physiological effect was expressed by the equation:

$$E_p = E_h + E_s + E_r + E_w$$

where  $E_p$  is the "index of physiological effect"; and  $E_h$ ,  $E_s$ ,  $E_r$ , and  $E_w$  are the environment's effects on heart rate, skin temperature, rectal temperature, and rates of sweating respectively. These partial indices are in the general form:

$$E_x = \frac{100}{x_2 - x_1} (x_3 - x_1)$$

where  $x$  is heart rate, skin temperature, rectal temperature, or rate of sweating;  $x_1$  refers to its value during a given grade of work in a cool environment;  $x_2$  refers to its value during the same grade of work at the most severe environment tolerable for two hours; and  $x_3$  refers to its value during the same grade of work in the environment to be evaluated. Observations covered a wide range of wet and dry bulb temperatures, but only a single wind velocity. This formulation should be of considerable value in studies on the heat stresses of the environment, and Robinson and colleagues have applied it in the study of hot weather clothing (34).

The objective of the group at Fort Knox was to delimit the environments which are compatible with effective physical work (35). Fully acclimatized and fully hydrated subjects marched at a fixed pace on the level during each exposure of four hours. Wet and dry bulb temperatures were varied independently from exposure to exposure. Physiological observations included pulse rate, rectal

and skin temperatures, and rate of sweating, but the practical conclusions were based on duration of effort before the onset of incapacity to work. Multiple criteria were used to define exhaustion. It was either the point of collapse, the point at which the subject had intolerable symptoms, or the point at which the observers felt it necessary to stop for humanitarian reasons. Dry bulb temperatures were from 93° to 121° F. and wet bulb from 90° to 96° F. Within these ranges the wet bulb temperature was the limiting factor on ability to work, dry bulb temperature exerting only a minor influence. As the upper environmental limits were approached a narrow range of wet bulb temperature, only about 4° F., separated environments in which work was fairly easy from those in which it was impossible. "Moderate" environments had wet bulb temperatures below 91° F., "severe" from 91° to 94°, and "intolerable" above 94°. These limiting wet bulb temperatures were about 2° lower when the dry bulb temperature rose from 100° to 120° F. Two phenomena of great interest were observed. First, exceedingly high values were reported for rates of sweating, probably the highest reliable values to be found in the literature. The highest value was 4.2 l. per hour, and rates of 3.5 to 4.0 l. per hour were not unusual. Second, an unusual syndrome was observed in which men sweated more water than they could absorb from the gastrointestinal tract, no matter how fast they drank. They became sick; bloating, nausea, and cramps occurred, and vomiting produced complete disability.

It should be emphasized that the work of both Robinson *et al.* (34) and Eichna *et al.* (35) applies to fully acclimatized subjects who are fully hydrated, and does not include observations on solar radiation which can cause a considerable increase in metabolic rate and also traumatic effects (36, 37, 48).

*Clothing.*—Research on clothing suitable for hot environments has received a great stimulus from military operations in the dry and moist tropics. However, very little of the work has been released for publication and discussion will have to be in generalities, with examples drawn from native customs. A compromise has to be made between comfort and protection. In the desert, evaporation of sweat is in the daytime the sole avenue of heat loss because the gradients for radiation, conduction, and convection are unfavorable. The loose Arabian costume allows evaporation to proceed effectively and yet protects from trauma by radiation, dust, thorns, and insects. Similarly the costume of the cowboy of

the Arizona-California desert region is physiologically satisfactory. In contrast to the desert, the jungle environment usually allows heat loss by radiation, convection, and conduction, but the high relative humidity hampers loss of heat by evaporation. However, not until the relative humidity is 100 per cent does evaporation cease to be an important avenue of heat loss, and it is particularly important for men who are working strenuously (38, 39). Native practice is to wear little or nothing in the jungle, but white men have to be protected against the jungle's flora and fauna in order to prevent injury and disease. The problem of clothing is far more difficult of solution in the jungle than in the desert. The most unfavorable conditions of all are met where workmen have to be protected against chemicals by the use of impermeable garments. Under these conditions all avenues of heat loss are hampered, evaporation of sweat is impossible, and the workman even in temperate environments may suffer from intolerable cardiovascular difficulties.

#### NUTRITION

*Dehydration.*—Nutritional factors important in the heat are listed in Table I, 3a through c. There is good agreement among different observers on the very rapid deterioration that ensues in the heat after deprivation of water. Within a matter of hours even the toughest, best acclimatized man becomes seriously inefficient, and eventually will succumb to "dehydration exhaustion" (30, 31, 40 to 43). Clinically this type of exhaustion is indistinguishable from the exhaustion of the unacclimatized individual, but chemically there is definite hypohydremia, with increased concentrations of hemoglobin and plasma protein and usually a slightly elevated plasma chloride (40, 41). Ingestion of adequate amounts of water prevents or long delays the onset of exhaustion; and in either dry or moist heat there is almost a direct linear relation between the amount of water drunk and the physiological benefits thereof. It is a rather surprising but well substantiated finding that the normal thirst response does not insure that the working subject will ingest enough water to give him maximal protection against dehydration during work (31, 41). Even when unlimited water is available, the average subject during the first day or two of acclimatization voluntarily incurs a substantial water deficit during work. After acclimatization is complete his water intake during work more nearly approaches his rate of sweating but he rarely voluntarily drinks during work more than two-thirds of the water

he has lost in sweat; the rest is replaced in the period after work is over. Nevertheless, if by forcing fluids, he does maintain his water balance from hour to hour he achieves maximal comfort and efficiency and minimal displacement of his total homeostasis. One possible explanation for the above findings on thirst is offered by the hypothesis of Dill that thirst is directly related to an increased osmotic pressure of the intercellular fluid (49). If the sweat has the same composition as intercellular fluid, dehydration is not accompanied by thirst. On the other hand, the more dilute the sweat, the more intense the thirst caused by a given water debt. For men performing a fixed task in a fixed environment, as in most laboratory studies, acclimatization is accompanied by a diminution of the sodium and chloride concentrations in the sweat. Hence, one would expect that the loss of one liter of sweat would be accompanied by more thirst after acclimatization than before but that the loss of one liter of sweat after acclimatization would not cause the individual to drink one liter of water because the sweat never becomes entirely devoid of sodium and chloride.

No attempts to prevent or alleviate the ill effects of rapid dehydration by the use of drugs have succeeded (42). In the heat treatment of central nervous system syphilis, extract of whole adrenal cortex but not desoxycorticosterone acetate was of benefit in minimizing the unpleasant symptoms and in accelerating recovery from the effects of heat (50). On the other hand, in the case of healthy working young men massive doses of extract of whole adrenal cortex had no effect on heat balance either in dehydrated or in well hydrated individuals (51). In both of the above studies on the effects of adrenal cortex, there was suggestive evidence that under equivalent physiological conditions the extract lowered the concentration of sodium and of chloride in the sweat, and Ladell (52) has reported this effect for desoxycorticosterone acetate. These observations may offer some insight into endocrinological factors controlling the action of the sweat glands and suggest analogies between the sweat glands and the kidney in their manner of secreting sodium.

Attempts to train acclimatized subjects to withstand dehydration and to alleviate the effects of dehydration by administering drugs have not succeeded (43). A tough subject can stand a lot of physical hardship, but the effects of significant dehydration are just as serious for him no matter how many times he has undergone dehydration. There is unanimous agreement among investigators



that the ideal to be aimed at in the field is frequent adequate water intake. It is fully appreciated that problems of supply may prevent the realization of this ideal but water should not be withheld on the grounds that it is bad for the worker, or that dehydration toughens a man.

The above discussion of dehydration is concerned with short term and rather acute conditions of deprivation. There is some evidence in the literature of exploration in the dry tropics and a widespread feeling among some officers with extended experience that if water supplies are cut down very gradually men can get along in a matter of months on a water intake that would have been totally inadequate at first (53, 54). However, there have been no conclusive laboratory or field observations on this particular aspect of the physiology of heat, and at present it seems desirable to adopt the conservative attitude that adequate hydration is indispensable for maximal efficiency.

*Inorganic substances.*—Of all the inorganic nutrients, sodium and chloride appear to be the only two whose deficiency can lead in a short time to serious consequences in the heat. There is reasonable agreement that a daily intake of about 20 gm. of salt is sufficient for most men in most environments. The experiences of Ladell *et al.* in the extremely severe conditions of the Middle East led them to recommend considerably more than this (45). They stress the great individual differences that exist and point out that men with abnormally high rates of sweating, abnormally high sweat chloride, or both may require as much as 50 gm. a day to avoid trouble. Conn & Johnston (55) recommend a maximum of 10 to 15 gm. on the basis of experiments in which men remained in balance on 5 gm. daily. However, it must be noted that their environmental conditions were mild, that the daily loss of sweat was only from 4 to 9 l., and that their subjects were few and were performing work in a steady state without the spurts of work common in daily life with consequent raising of skin temperature and sweat chloride. The whole experience of tropical medicine and industrial physiology is arrayed in favor of rather than against a fairly high intake of salt if trouble is to be avoided in all men (56). The institution of salted drinking water by industries and the subsequent "salt discipline" of the army have caused heat cramps to become a minor problem for them as is shown by the greatly lowered incidence of casualties. It would seem unwise to take any chances with this present desirable condition.

*Other requirements.*—Other nutritional considerations are probably much the same in temperate and in hot environments. Caloric requirements for work are not much affected by heat and the voluntary caloric intake of U. S. soldiers did not show any significant seasonal variation (57). Within wide limits alterations in the dietary ratio of fat, carbohydrate, and protein have little practical significance. The theoretical objection to a high protein diet in hot weather is that the high specific dynamic action of protein puts undue stress on the heat dissipating mechanisms, but under field conditions this objection is of little importance for several reasons. First, working men relish a high protein diet. For example, the average daily intake of protein by U. S. troops even in the moist tropics was close to 125 gm. protein when food was readily available (57). Second, laboratory observations showed that wide variations of dietary protein had no significant effect on the feelings or performance of subjects working in the heat (58). Third, closer scrutiny of the premises reveals the fallacy that if an active subject is able to maintain heat balance at all, any extra heat load due to protein is physiologically insignificant in comparison with his caloric expenditure. The question of the optimal intake of vitamins is just as controversial for the heat as it is for temperate conditions. Although there is clear evidence that large extra supplements of the water soluble vitamins are of no measurable benefit to men subsisting on an unquestionably good daily diet (41, 59), there is disagreement as to the daily requirements for the vitamins. Mills (60) takes issue with several workers including Holt (61), Keys (62), and Johnson (46), all of whom have concluded that there is no convincing evidence in favor of increasing vitamin intakes in the heat. He distinguishes between vasomotor acclimatization, taking days, and metabolic acclimatization, requiring weeks and involving profound changes in cellular oxidations and the endocrine system. He claims that there is a greatly increased requirement for thiamine and choline. There is justice in Mills' argument that observations on human subjects have not been systematic or prolonged enough to arrive at complete answers for hot environments. Kline, Friedman & Nelson disagree completely with Mills' conclusions concerning thiamine (63).

Clinical knowledge of the ill effects of heat has been expanded during military operations in the desert and jungle. Heat stroke, characterized by extreme hyperpyrexia, cessation of sweating, coma, and death usually from right sided heart failure and pulmo-

nary congestion, was fairly frequent in the desert but almost non-existent in the moist tropics. Two fairly constant chemical findings were a state of normal hydration and a normal chloride balance (45). These findings relegate water and salt to a secondary place in the treatment of patients, the primary consideration being the immediate lowering of the body temperature. A constant prodromal sign is reduction or cessation of sweating (45, 64). Suggestions have been made that this is an accentuation of the normal course of sweating during prolonged work, in which there is a progressive and considerable falling off in the rate of sweating from hour to hour regardless of the subject's state of water balance (41). If this reduction went far enough, it could result in hyperpyrexia (64). Too rigid classification of the ill effects of heat is perhaps unwise because men exposed to the many vicissitudes of hot environments may become ill and show elements of all of the syndromes hyperpyrexia, heat cramps, and exhaustion. Ladell *et al.* (45) recognized two fairly distinct types of exhaustion in Southern Iraq. Type I occurred early in the summer, was characterized by vomiting, cramps, and orthostatic hypotension, and was a salt-deficiency dehydration. Type II occurred late in the summer, and was characterized by defective sweating and polyuria, by miliaria, and by lack of hyperpyrexia, vomiting, cramps, or cardiovascular abnormalities. It appeared to be a general breakdown of the body's defenses against heat.

There is little definite knowledge on the etiology of the syndrome "tropical deterioration," or on the relative importance in it of neuropsychiatric and physiological factors. In ordinary times white people who dwell in the tropics usually do so from choice and because of strong economic, social, or religious motives. The war placed in the tropics millions of men who had no particular interest in them. The syndrome of tropical deterioration usually includes: poor physical condition; chronic fatigue states; sometimes chronic diseases; deterioration in character, memory, initiative, and responsibility; and a variety of psychosomatic complaints (65). Treatment consists of frequent change of scene; intensive programs of exercise, recreation, and education; and in the worst cases evacuation to temperate climates. Prevention consists of adequate selection of men to go to the tropics, and good programs of duty, exercise, recreation, and education.

## COLD

Physiological reactions to cold have been the subject of intensive research, but publication in this field has been far more restricted than in hot weather physiology. Much emphasis has been placed on clothing and protective equipment, because conservation of stored heat is a necessity for efficient performance in the cold. The protection afforded by any assembly of clothing depends in part upon the functional properties of the materials themselves and in part upon the reaction of the wearer to the whole assembly. A volume edited by Newburgh & Harris (66) summarizes principles and methods applied during the war to test clothing.

The physical properties of clothing which interest the physiologist include: tensile strength, tear strength, abrasion, shrinkage, flexural rigidity, flexural fatigue, flame proofing, flash resistance, frictional properties, water repellency, buoyancy, thickness including compressibility and compressional resilience, effective pressures inside the clothing, resistance to diffusion of water vapor, rate of drying, air permeability, and thermal insulation. There are approved methods for determining all of these, with general agreement among textile industries, industrial research institutes, and government laboratories (67).

Whatever other properties an adequate cold weather assembly must have, it must provide adequate insulation against the environment to which the subject is exposed. The principles of measuring insulation are discussed by Burton (68), by Hardy & Dubois (69), by Winslow, Gagge & Herrington (70), and by Gagge, Burton & Bazett (71). For human subjects the heat loss ( $H_{cl}$ ) through a clothing assembly is equivalent to the sum of metabolic heat production ( $M$ ) and heat lost through cooling of the body tissues ( $D$ ) after subtraction of heat loss via the lungs in vaporization of moisture ( $E_l$ ) and warming the inspired air ( $A$ ), and heat loss through vaporization of perspiration at the skin ( $E_s$ ). That is,

$$H_{cl} = M + D - (E_l + E_s + A)$$

Laboratory procedures for determining  $H_{cl}$  are discussed by Belding *et al.* (67).  $M$  is measured by direct or indirect calorimetry over a period of at least three hours.  $D$  is measured according to Burton (68), the mean temperature of the body ( $T_b$ ) being calcu-

lated from the rectal temperature ( $T_r$ ) and the weighted mean of the temperature of eleven points on the skin ( $T_s$ ).

$$T_b = 0.33T_s + 0.67T_r \quad \text{and}$$

$$D = T_b \times 0.83 \times W,$$

where  $T_b$  is the change in temperature of the body, 0.83 is the assumed specific heat of the body, and  $W$  is the body weight.  $E_i + E_s$  is approximated from the equation:

$E_i + E_s = [\Delta W - (0.30 \times \text{oxygen consumption in gm. per hour}) \times 0.58]$  where  $\Delta W$  is net change in body weight to the nearest gram; 0.30 is the factor for converting oxygen consumption to excess carbon dioxide excreted over oxygen consumed; and 0.58 is the heat of vaporization of water. Alternatively,  $E_i$  may be calculated from pulmonary ventilation ( $V$ ) by the equation:

$E_i = V \times 0.0242$ .  $A$  may be calculated from the equation:

$A = (T_{\text{expired air}} - T_{\text{inspired air}}) \times 0.0031 \times V$ , where  $T$  is air temperature; 0.0031 is the specific heat of air; and  $V$  is the pulmonary ventilation. All values are eventually expressed in terms of kcal. per sq. m. per hr.

After  $H_{cl}$  is determined the thermal insulation of the outfit is calculated from the fundamental equation:

$$\text{Insulation} = T/H,$$

where  $T$  is the temperature difference between any two surfaces and  $H$  is the heat flow between. When insulation is to be expressed in  $Clo$  units ( $I_{clo}$ ) the formula used is

$$I_{clo} = \frac{3.09 (T_s - T_a)}{H_{cl}} - I_a,$$

where  $T_s$  is the average skin temperature and  $T_a$  is the ambient temperature, both in Fahrenheit degrees; and  $I_a$  is the insulation of the air at the experimental wind velocity, according to the formulation of Burton (71).

The many precautions necessary in clothing tests are discussed by Talbott (72). Subjects must be standardized according to age, medical history, training acclimatization, quartering, pretest conditions, time of day, clothing, activity, and fit of gear. Clothes and gear should be dried at a fixed relative humidity. Even when all precautions are taken, duplicate estimations agree at best to about 15 per cent.

In outfitting men for the field, adequacy of an outfit is difficult to define, owing to such variables as degree of activity, time of exposure, and severity of environments (73). *Clo* values are a useful guide but should not be considered an absolute index of insulation for at least three important reasons. First, if there is uneven distribution of insulation the *Clo* value may be high, but intolerable local cooling of poorly insulated areas may diminish the adequacy of the outfit (74). Second, accumulation of water in the clothing may markedly diminish the insulation of an outfit. This is a well established principle of the explorers, who take great precautions to prevent it (75), and quantitative studies in the laboratory have shown the extent of the effect (76). Third, movement increases loss of heat by convection so much that the *Clo* value of an outfit worn by a sitting subject can decrease by two-thirds when he walks (77). Nevertheless, for predicting clothing requirements the *Clo* is useful, since it is a measure of insulation for the resting subject, and maximal protection is required by men during periods of inactivity in the cold. They can always cool themselves off during periods of activity.

The literature on nutrition for cold weather consists of a relatively large body of writings by explorers and others who have lived in Arctic and subarctic regions, and of a small series of systematic observations by trained nutritionists in the laboratory and in the field. There can be little disagreement on the necessity of maintaining adequate water, caloric, and salt balances. In the absence of definitive studies it appears sound to consider vitamin requirements to be much the same in temperate and cold climates. It is probable that the proportions of fat, carbohydrate, and protein in the diet are important. One would expect a preference for foods of high caloric density, because caloric expenditures for identical types of work are higher in cold than in temperate climates, partly because of increased caloric expenditure to maintain heat balance at rest and partly because of increased burden of clothing and difficulties in locomotion. Explorers agree that a high fat diet is preferred and beneficial (75). Laboratory studies have shown that subjects exposed to cold maintain heat balance best when the proportion of fat in the diet is high, and worst when the proportion of protein is high (78). In addition, they are better off on many small meals than on a few large ones.

Claims have been made that the best diet for the Arctic consists principally or even solely of animal flesh and animal fat (75), and

there has been considerable discussion of pemmican which consists of dried meat and fat in approximately equal proportions by weight. It has been little used in the packaged rations of the war, but there is a long tradition of its successful use by Indians, travelers, and explorers (75). The chief reason why it has not been issued to troops is its unacceptability to the average individual. This is in contrast to the explorers who, it must be remembered, were a picked group willing to tolerate exceedingly unpleasant conditions in the furtherance of their aims. The only published field study of pemmican by systematic methods clearly illustrated several points of general interest: the overwhelming importance of acceptability in packaged rations; the dramatic suddenness and extent to which nutritional difficulties can develop in a few days; and the manner in which historical errors can be perpetuated (79). A platoon of infantry, well trained and acclimatized during maneuvers under subarctic conditions, received a ration consisting solely of pemmican and tea. They found it unacceptable, ate only about 1500 Calories a day when they were expending about 4500, and within three days were tactically useless, showing exceedingly poor physical fitness, ketonuria, ketonemia, hypochloremia, and dehydration. The same pemmican proved acceptable when supplemented with biscuits, oatmeal, salt, and sugar, and during the next five days they recovered most of their tactical effectiveness. A search of the literature revealed that insofar as published accounts will allow a semiquantitative estimate, no exploring party either in the Arctic or Antarctic has ever thrived on pemmican without a carbohydrate supplement; and in fact, when very high percentages of pemmican have been included, sickness or disaster has been the lot of the expedition. It was concluded that, as a short term assault ration for infantry troops, pemmican alone is unsatisfactory (79).

#### PHYSIOLOGICAL OBSERVATIONS IN THE FIELD

The testing of many new items of clothing, protective equipment, and personal equipment was assisted during the war by physiologists. Laboratory observations under controlled conditions can settle such questions as the relative insulation of two outfits of clothing. However, the adequacy of an assembly depends on many other factors, such as comfort of fit, ease of use, durability, and drying properties, and these are best tested in the field. Information can then be gained by systematic observations on the per-



formance of the men, on the state of equipment after use, and by the reactions of the men to the equipment (80).

Another reason for field observations was to assist in protecting men working in severe environments or exposed to possible toxic agents such as drugs, gun fumes, and carbon monoxide. Such observations were made by all branches of the armed forces, but very few of the studies have been released for publication.

A final example of field observations is as an adjunct to surveys the purpose of which is to detect and combat deterioration (81, 82). The possible causes of physiological deterioration are so various that usually many different but related factors have to be examined systematically. Information can be gained by a variety of methods. Interviews, questionnaires, and inspection determine the state of supplies, equipment, protective devices, clothing, and rations. Medical histories disclose symptoms of abnormal physical states and in addition give insight into neuropsychiatric disturbances. Physical examinations disclose signs of disease. Tests of physical fitness are useful for examining the condition of men expected to perform physical work. Chemical and physical measurements assess important phases of biochemical and physiological status. Whatever techniques are employed should be so standardized that results are directly comparable from place to place even when obtained by different groups of observers.

Experience in the war (81) demonstrated that field surveys on troop nutrition can most successfully be conducted by teams one or more of whose members has special training in each of the following: (a) biological statistics and sampling techniques; (b) procurement and supply with emphasis on personal equipment, clothing, and rations for various environments; (c) clinical medicine including nutrition and environmental physiology; it is desirable to have the help and advice of persons familiar with the general problems of areas to be visited, especially in the tropics; and (d) laboratory techniques both chemical and physical for assessing the biochemical and physiological status of subjects examined. It is essential to have a smoothly functioning portable laboratory with equipment and methods suitable for use in the field (83).

Satisfactory diagnoses may be difficult to reach, although when all sources of information point in the same direction conclusions can be drawn with reasonable certainty. As often as not there is a complicated and confused situation in which no certain conclusions

can be reached. Scientifically satisfactory control subjects may be difficult to find, principally because all men in a given area are usually subjected to much the same stresses. In such cases it becomes necessary to use for control purposes observations made in different places. Even when well-founded conclusions can be drawn local problems of supply, equipment, or other practical hindrances may prevent satisfactory implementation of recommendations.

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## PHARMACOLOGY

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In selecting material for this review on pharmacology the aim has been to concentrate on several subjects rather than attempt to cover the field as a whole. The topics discussed are more or less related in that they are all concerned, at least to a certain degree, with enzyme activity. It will be obvious to the reader that even within the restrictions of the narrow field selected, space considerations have necessitated the omission of discussion of many papers equally as worthy of presentation as those summarized here.

### ENZYMES IN DRUG ACTION

Enzymology, although comparatively a rather young science, is serving as a tool not only for the physiologist in determining various physiological processes but also for the pharmacologist in the elucidation of the mechanism of action as well as the inactivation of drugs. Drugs may conceivably exert their effect by serving as substrates for enzymatic action or they may affect the intrinsic activity of enzymes. Some of the more recent investigations of this nature on several groups of therapeutic agents will be reviewed.

### RELATIONS BETWEEN HORMONES AND ENZYMES

Very little information is available regarding the effect of the various hormones on enzymatic reaction. To date most of the published work is concerned with the influence hormones may have on the enzyme action of various glands and tissues. These studies have been both of an *in vitro* and an *in vivo* nature. In this review the effects of the active principles of several endocrine glands as well as of the glands themselves on various enzyme systems will be presented.

*Thyroid.*—Much work has been carried out to determine the effect of the thyroid hormone on the various respiratory systems. Rossiter (1) reports that brain brei from rats treated with thyroid and thiamine in the presence of glucose, sodium pyruvate, or sodium succinate has a higher oxygen uptake than brei from control rats receiving thiamine only. Spirtes (2), on the other hand, found that feeding desiccated thyroid to guinea pigs had no effect on the

oxygen uptake of brain slices from this animal. However, the oxygen uptake was increased in liver and kidney slices.

A decrease in the *d*-amino acid oxidase in the tissues of thyroidectomized rats and an increase in the tissue of rats maintained on an adequate diet plus thyroid tissue has been reported by Klein (3, 4). Williams & Watson (5) observed an increase in the bone phosphatase in animals following thyroxine administration.

More recently Tipton *et al.* (6) reported that daily feeding of desiccated thyroid to rats increased the total succinic acid oxidase and the cytochrome oxidase activities of the liver, the effect on the former being the greater. It is of interest to note that they report a similar but weaker effect from the subcutaneous administration of thyroxine in a daily dose of 0.5 mg.

Paschkis *et al.* (7) found that the oxidase activity of thyroid glands was decreased by the addition of thiouracil *in vitro*. They also report that thyroid glands obtained from rats treated with thiouracil for a period of five days to four weeks definitely decreased the oxidase activity per unit weight of gland. It is believed that cytochrome oxidase is necessary for the synthesis of thyroxine and they suggest that the inhibition of oxidase activity may be a factor in the suppression of thyroid function through thiouracil.

This suggestion of the mode of action of thiouracil is compatible with the results of some studies recently reported by Halpert, Cavanaugh & Keltz (8). In some patients treated preoperatively with thiouracil, clinical manifestations of hyperthyroidism reached a minimum. Upon removal of the thyroid it was found that the cells of the acini had changed in character from cuboidal to columnar. The colloid had either entirely disappeared or had become less dense and vacuolated. It would appear, therefore, that the thiouracil had prevented or inhibited the production of new colloid, but had not interfered with the utilization of the available colloid.

*Adrenal hormones.*—A discussion of the interaction of the various hormones of the adrenals and enzyme systems may be divided into two sections—that dealing with the medullary substance and that concerned with the principles elaborated by the cortex.

The role that epinephrine plays in the accelerated breakdown of glycogen to glucose in the liver or of glycogen to lactic acid in the muscle has long been established. The enzyme systems involved in these reactions have also been elucidated and reviewed by Cori (9, 10, 11). Another phase of interest is the part played by

enzymes in the deamination or the metabolism of epinephrine. This will be referred to in a later section of this review.

Some studies have also been carried out to determine the effect of the cortex on some of the enzyme systems. Some of the earlier work of this nature has been reviewed briefly by Jensen & Tenenbaum (12). Tipton (13) found that liver slices obtained from adrenalectomized rats showed a slower rate of respiration in the presence of sodium succinate and sodium pyruvate. This suggests that there might be hormonal regulation of the respiratory enzymes involved in the oxidation of these substances. Since both cytochrome oxidase and the substrate cytochrome-*c* are involved, Tipton (14) more recently studied the effect of adrenalectomy on the concentration and activity of these substances. There was a significant decrease in cytochrome oxidase activity in nearly all the tissues studied in the untreated adrenalectomized rat and there was also a decrease in the cytochrome-*c* concentration in the liver and kidney. Treatment with sodium chloride prevented the decrease partially, whereas adrenal cortical extract (Eschatine) prevented the decrease almost entirely. These decreases appear at the same time that one finds the decreased respiratory response to excess succinate and pyruvate added to the tissue. It is suggested that the decrease in oxidase may possibly play some part in the total decrease.

It will be recalled that mention was made above that feeding desiccated thyroid or the subcutaneous administration of thyroxine increased the succinic dehydrogenase and cytochrome oxidase activity. In the same publication Tipton (14) reports that four to ten days after adrenalectomy there is a decrease in the activity of both of these enzymes. Of the two, cytochrome oxidase is affected more markedly. Furthermore, if the adrenals are removed from rats after they have been fed thyroid for seven to twelve days, there is no further increase in enzyme activity. Thus these studies give further evidence of the relation of the adrenal cortex to cytochrome oxidase activity.

Kochakian & Vail (15) report an increase in the alkaline phosphatase of the liver of rats as a result of either adrenalectomy or administration of an extract of the adrenal cortex. The acid phosphatase of the kidney is decreased but returns to normal on administration of adrenal cortex extract. The alkaline phosphatase of the kidney is not altered by adrenalectomy.



It is known that certain  $C_{11}$  oxygenated cortical hormones will cause glycconeogenesis from protein and it is suggested that the increase in alkaline phosphatase of the liver, as described, may indicate that the adrenal cortex affects carbohydrate metabolism by way of the phosphorylated intermediates.

*Sex hormones.*—Although estrogens and androgens undoubtedly affect metabolism either directly or indirectly, there is at present very little information regarding their effect on the various enzyme systems.

Androgens stimulate protein anabolism, an effect which is accompanied by retention of phosphorus. Knowledge of this suggested the study of the effect of testosterone propionate on enzymes concerned with phosphate metabolism. Kochakian & Fox (16) studied the effect of castration and of testosterone propionate on the alkaline and acid phosphatases of the kidney, liver, and intestine of mice. The liver and intestinal phosphatases showed very little change but the enzymes of the kidney were definitely affected both by castration and testosterone propionate therapy. Castration alone resulted in a decrease in the alkaline as well as the acid phosphatases. The decrease in both cases was in about the same proportion as the decrease in the kidney weight. In normal or castrated mice treated with testosterone propionate there was a decrease in the alkaline phosphatase and an increase in the acid phosphatase. The latter increases with an increase in the period of treatment. It is of interest to note that the respective enzymes were altered similarly by the testosterone propionate regardless of whether the mice were normal or castrated. At present it has not been determined in what structures of the kidney these phosphatase changes occur. It is suggested that the kidney increases its acid but decreases its alkaline phosphatase to retain sufficient phosphorus to meet the metabolic demands resulting from the administration of testosterone propionate.

The relation of arginase activity to protein metabolism and the knowledge that urinary androgen extracts produce nitrogen retention suggested an investigation of the effect of various steroids on arginase activity. Kochakian (17) studied in mice the effect of castration and of administration of various steroids on the arginase activity of several tissues. The steroids were administered as pellets implanted subcutaneously thirty days after castration. Observations were made after ten or thirty days treatment. It was found

that none of the steroids had any significant effect on the arginase content of either the liver or the intestine. The kidney showed an increase in concentration of arginase following castration rather than in the total content. A further increase in kidney arginase was observed following the administration of a number of the steroids provided these steroids enlarged the kidneys. There was no direct relation between increased kidney weight and arginase activity. On the basis of experimental evidence it is suggested that the increased arginase activity is due to an increase in the content and not to the production of an activator.

At present it is not possible to attribute any specific role to the increased arginase activity. The steroids that produce the greatest activity also decrease the blood and urine urea. It is apparent, therefore, that the resultant increased enzyme activity is not concerned with the formation of more urea by the Krebs-Henseleit cycle. It must therefore be assumed that the anabolic effect of steroids is through other amino acids.

Much of the reported work on the relation of estrogens to enzyme systems has been concerned with the identification of estrinase, the estrone-inactivating enzyme. It has been demonstrated that estrone may be inactivated *in vitro* by liver and spleen as well as by hyacinth root and that this effect is clearly enzymatic. The inactivation of estrone has also been carried out by other substances such as red beets, bran, potatoes, and mushrooms. There has been some confusion as to the identity of the enzyme responsible for the inactivation, especially the relationship between tyrosinase and estrinase. Zondek & Finkelstein (18) have recently investigated this relationship, employing a highly purified tyrosinase preparation obtained from potatoes to determine the relationship of monophenol and polyphenol oxidase to estrone inactivation. Since the purified tyrosinase obtained from potatoes was inactive toward estrone, it would appear that the estrone-inactivating principle in potato extract is not identical with tyrosinase, in agreement with previous observations (19).

Graubard & Pincus (20) found that the mushroom preparation of Westerfeld inactivated estrone and ascribed this activity to the presence of laccase. The crude potato extract employed by the present authors contained no laccase and, therefore, the estrone-inactivating effect could not be due to the latter. Likewise from these results it would appear that tyrosinase and estrinase activity

are not necessarily linked. On the basis of their results two possible explanations are suggested:

"(1) that estrinase and tyrosinase are distinct and separate enzyme systems;

"(2) that estrinase is a system composed of tyrosinase plus a further heat-labile factor."

The authors do not indicate any choice between the two possibilities.

#### SYMPATHOMIMETIC AMINES

An extensive series of studies has been reported on the relation between various enzyme systems and a large number of sympathomimetic amines to elucidate their metabolism and elimination.

Beyer & Morrison (21) have recently reviewed this subject so extensively that the reader may refer to their publication for details and references to original articles. Only a short synopsis of their report will be presented at this time.

Some of the enzyme systems which might be concerned in the deamination and inactivation of the amines follow. Tyraminase or amine oxidase, which is present in many of the mammalian tissues, is capable of deaminating phenethylamine as well as certain of its derivatives and some aliphatic amines.

Phenol oxidase or tyrosinase has been isolated in a highly purified state from potatoes as well as mushrooms; however, its presence in mammalian tissue has not been established with certainty. This system is capable of oxidizing tyrosine, tyramine, and compounds having the catechol nucleus. Phenol oxidase in the presence of *p*-cresol is also able to deaminate amphetamine *in vitro*. In addition, the ascorbic acid-dehydroascorbic acid system has been shown capable of deaminating some of the amines such as phenethylamine and some of its derivatives. The phenethylamine is not as rapidly deaminated as tyramine. The addition of one methyl group on the  $\beta$ -carbon has little effect, whereas a longer chain or two methyl groups in this position decreases or abolishes deamination completely. Alkyl substitution on the amino nitrogen affects the rate of deamination variously, depending on the type of substitution. Converting the primary amine to a secondary methylamine increases the rate of deamination, whereas increasing the length of the alkyl chain or converting it to a tertiary amine ne-

gates this effect entirely. The position of the amino group on the side chain also is of importance as deamination is completely abolished when this group is removed from the terminal carbon.

The effect of the addition of an hydroxyl group in the ring is dependent upon its position. If this group is placed in the meta position there is a marked increase in the rate of deamination, while if placed in the para position the deamination is completely abolished. Of all the compounds studied the catechol derivatives of phenethylamine were most rapidly deaminated. In general there was a good correlation between pressor action, duration of action, effectiveness following oral administration, and excretion of phenethylamine derivatives and their deamination.

More recently Snyder, Goetze & Oberst (22) reported results of metabolic studies on  $\beta$ -phenethylamine and some of its derivatives. Their observations included (a) the rate of deamination in the presence of liver amine oxidase and (b) the extent of excretion in the white rat following subcutaneous administration. Their results confirm the observations of others on the relation of structure to the rate or degree of oxidation by amine oxidase. In the excretion experiments it was shown that the compounds oxidized by amine oxidase are eliminated only in small part in the urine.

It had been reported previously that mescaline was attacked very slowly by amine oxidase obtained from guinea pig liver whereas it is readily oxidized if the enzyme is obtained from rabbit liver. The relatively high tolerance of rabbits to mescaline has been assumed due to this finding. Bernheim & Bernheim (23) reported that the deamination of mescaline differed from that of typical substrates of amine oxidase in that the oxidation is inhibited by cyanide. On the basis of their studies they concluded that amine oxidase plus a cyanide-sensitive factor are necessary. Blaschko (24), on the other hand, has suggested that amine oxidase is not concerned in the oxidation of mescaline. He bases this assumption on some differences in the oxidation of this amine and of *l-p*-sympatol, which is a typical substrate of amine oxidase. Among these differences is the fact that secondary octyl alcohol, which is a strong inhibitor of amine oxidase, does not interfere with the oxidation of mescaline. Likewise, methylene blue interferes only slightly with the oxidation of the latter, whereas it completely inhibits the sympatol oxidation.

## ANTIBIOTICS

The impetus given to the study of antibiotics by the immense interest in penicillin has led to numerous investigations of the mechanism of antibiotic action. During the course of this experimentation some information on the relationship between several antibiotic substances and various enzymes or enzyme systems has been obtained.

At the present there is not sufficient information available to make a conclusive statement in regard to the mode of action of either gramicidin or tyrocidine. No demonstrable relationship to any enzyme system has yet been found. As far as the effect of some enzymes on these two substances is concerned it has been shown that they are not hydrolyzed by crude trypsin, pepsin, papain, and papaya latex. Hotchkiss (25) reported that, as a result of such treatment, there was no increase in free amino or carboxyl groups. Lipmann *et al.* (26) suggested that the resistance to this enzymatic hydrolysis might be attributable to the *d*-amino acid content of these substances.

Clavacin, another substance having antibiotic activity, is of interest here because of the effect it has on many of the respiratory enzymes. According to Happold & Waters (27) this antibiotic completely inhibits glucose dehydrogenase, succinoxidase, malic acid dehydrogenase,  $\alpha$ -glycerophosphate dehydrogenase, and tryptophanase. Other oxidative enzymes such as lactic acid dehydrogenase and *d*-amino oxidase were only partially inhibited. Enzymes such as vegetable tyrosinase or the proteolytic enzymes trypsin and pepsin were not affected.

Most of the investigations of this nature have been carried out with penicillin. Abraham & Chain (28) in 1940 reported that an agent was elaborated by *Escherichia coli*, as well as by some other bacteria, which destroyed penicillin. Because of its enzymatic nature this substance was designated penicillinase. Since that time the production of such an agent has been verified by other investigators. It was also reported that Clarase, a diastatic enzyme preparation, inactivates penicillin (29). Later studies (30, 31) showed that the penicillin-inactivation was related not to the diastatic enzyme activity, but to the presence of bacterial metabolic products, principally those from *B. subtilis* and other related gram-positive organisms.

In the earlier studies unsuccessful attempts were made to obtain a penicillin inactivator from either sensitive or resistant staph-

ylcocci. More recently a penicillin-destroying staphylococcus has been reported from several sources (32, 33). Kirby (34) investigated the properties of an inactivator extracted from penicillin-resistant staphylococci and compared it with some of the other known penicillin inactivators of bacterial origin, finding only minor differences. Spink & Ferris (35, 36) reported some studies on a penicillin inhibitor from staphylococci which had developed resistance to penicillin in the human body. The inhibitor was absent, however, in several strains of staphylococci which had been made penicillin-resistant *in vitro*.

Chow & McKee (37) have studied the chemical aspects of penicillin-inactivation and found that cysteine is capable of abolishing the activity. They suggest that the chemical reaction may involve both the sulfhydryl and amino groups.

Cavallito *et al.* (38, 39) have investigated the inactivation by cysteine of a number of antibiotic substances and have formulated a theory of the mode of action of these agents. It is suggested that many of these antibiotic agents may act by reacting with the sulfhydryl groups of enzymes. Differences in the antibacterial action of the agents might thus be dependent upon their ability to come in contact with the essential sulfhydryl groups.

It has been the aim in this portion of the review to point out some of the relations between several groups of therapeutic agents and enzyme systems. The relation of the penicillin-inactivator to penicillin-fastness as well as the role of enzymes in sulfonamide action will be discussed below. It will be noted that the information regarding the way in which many of the substances discussed affect enzyme reactions is rather meager. Much of the available information has been obtained by *in vitro* experiments, and the results may be misleading in attempting to interpret responses of the living organism. The *in vivo* studies in many cases are limited to a single species of animal, so that caution must be exercised in making generalizations.

#### DEVELOPMENT OF RESISTANCE TO CHEMOTHERAPEUTIC AGENTS SULFONAMIDE-FASTNESS

In the initial phases of the sulfanilamide studies, cures of various bacterial diseases were secured in a very high percentage of patients. Since then there has been a tendency, for at least some infections, for the responses to be progressively less satisfactory

until, in the case of gonorrhea, considerable difficulty is now encountered in treating the infection through the use of any of the sulfa compounds. A characteristic set of data is that published by Carpenter *et al.* (40) on a continuous study of the treatment of gonorrhea in one community as part of a special program of public health. They observed that only 15 per cent of gonococcus cultures studied by them in the early part of 1942 were resistant to sulfonamides. In less than eighteen months this percentage had increased to 59.

The first question is whether sulfa-fastness is encountered in all organisms or is a peculiarity of response of only a limited number. No attempt has been made to explore the entire literature of this field to collect data on each individual organism against which "sulfas" have been used. However, fastness to the following organisms among others has been reported indicating that this property is fairly widespread: gonococcus (40, 41), pneumococcus (42, 43), hemolytic streptococci (44), brucelli (45), *E. coli* (45), and staphylococci (45, 46). These bacteria comprise some of the more important ones against which sulfa drugs are employed.

The conditions under which sulfa-fastness develops have been reproduced experimentally many times. As an example, Boak & Carpenter (41) exposed gonococci to gradually increased amounts of sulfanilamide and found that the lethal concentration was raised until organisms were finally able to withstand previously surely fatal amounts. When the organisms have once been made resistant to the sulfa drug they do not necessarily retain this fastness indefinitely, although they may do so. There is a difference between individual organisms in this respect, which so far has no very complete explanation. In studies on the streptococci, Cutts & Troppoli (44) found that resistance to sulfanilamide was maintained at a high level for one month, but spontaneously disappeared after about three months. For pneumococci, Schmidt *et al.* (45) found that resistance to sulfapyridine was retained by his strains through more than two hundred passages through mice. Working on gonococci, Westphal *et al.* (46, 47) have reported that nine out of ten cultures became resistant to sulfapyridine in twenty to twenty-eight days and that sulfapyridine-fastness persisted for at least two months after the organisms were removed from a sulfa-containing medium. Staphylococci were found by Spink *et al.* (46) to remain resistant to the sulfa drug for at least two years. Inas-



much as some strains of an organism do not become resistant at all, as evidenced by the references above, there would seem to be an inherent mechanism peculiar to the individual bacterium which determines whether the fast-state can be developed and, if so, how long it will persist under the conditions imposed.

Another question is whether resistance developed to one sulfa drug makes the organism equally resistant to others. Kirby & Rantz (45) reported that *E. coli* developed resistance which was demonstrated against all four of the sulfa drugs they tested, namely, sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. They postulated that all organisms susceptible to the bacteriostatic action of sulfonamides are capable of becoming resistant to all the sulfonamides. Westphal & Carpenter (48, 49) studied the crossed tolerance of organisms for sulfa compounds. They found that sulfapyridine-fast strains of gonococci grew well in a medium containing 0.055 per cent of sulfanilamide. However, sulfanilamide-fast strains tolerated only 0.02 and 0.03 per cent of sulfapyridine. Apparently for this organism, and the strains studied, the tolerance was conditioned by individual reactivities of the organisms involved. Lowell *et al.* (50), using pneumococci, reported that strains made tolerant in cultures to one of the "sulfas" also became resistant to the others studied to approximately the same extent. However, individual strains of organisms varied in the ease with which fastness was acquired.

Sesler & Schmidt (51) also observed that various strains of pneumococci varied in the ease with which they developed resistance. This variation may consist of changes in the rate at which a strain will develop resistance as well as in differences in the actual maximum concentrations of the drug against which resistance can be developed. In general, these latter authors found that resistance was developed most rapidly to the least effective drug and most slowly to the most highly effective drug. They also noted that resistance to one sulfa compound was associated in that organism with resistance to the other drugs they had under test.

It is probable that the mechanism of the development of fastness is directly associated with the mode of action of the sulfonamide compounds, which will be reviewed and discussed in a later section. One point, however, which may be considered here is whether the sulfa-fast state is simply an uncovering of naturally resistant organisms through killing off the more susceptible ones.

There is a natural variation in the sensitivity of the organisms to these chemotherapeutic compounds, as has been well summarized by Hill *et al.* (52). However, the degree of resistance which can be developed by appropriate means is greater than can be demonstrated for any individual organism present in the original culture when initial exposure to the drug is made. It would appear, therefore, that there is more to the development of the sulfa-fast state than just a weeding out of the more highly sensitive organisms.

Schmidt & Sesler (53) demonstrated that bacteria with increased resistance were created with each successive exposure of pneumococci to sulfapyridine. They were also able to differentiate between the sensitivity of normal and of sulfa-fast organisms, and the spontaneous variation in sensitivity encountered in normal populations. Kirby & Rantz (45) interpreted their results on sulfonamide resistance as indicating an interaction between the organism and the common structural unit of all the sulfonamides, namely, the *p*-aminobenzenesulfanyl nucleus. They suggested that this interaction might involve the same enzyme system as was concerned in the *p*-aminobenzoic acid relationship to sulfa action.

Spink *et al.* (46) were able to confirm the observations of Landy *et al.* (54) and Housewright & Koser (55) that the resistant strains elaborated an inhibitory substance which was tentatively identified with *p*-aminobenzoic acid. Reed *et al.* (56), working on *Clostridium*, found that the species which produced the largest amount of inhibitor were those against which the sulfonamides exerted the least bacteriostatic action. They pointed out, however, that slight bacteriostatic effects *in vitro* might be associated with marked anti-septic power *in vivo*, where the effects of sulfa drugs are reinforced by tissue constituents. That the tissues are not inert in this entire situation was also demonstrated by Boroff (57), who found that the sera of sulfa-resistant patients antagonized the action of sulfa drugs on sensitive organisms. Whether the substance in the serum responsible for this is *p*-aminobenzoic acid or some other metabolite was not established by the studies.

Under the influence of the sulfa drugs, changes in the morphological types of bacterial colonies may be developed, such as shifts between rough and smooth strains. However, Cutts & Troppoli (44) believe that such changes of phase, although simultaneous with sulfanilamide resistance, are not causally related and may vary independently. Along the same lines, MacLeod & Daddi (43)

report that pneumococci made resistant to sulfapyridine have no detectable changes in morphology, virulence, or specific immunological characteristics.

It would seem that the most popular theory of the cause of increased resistance is one of an increased ability of the organisms to synthesize *p*-aminobenzoic acid. However, there are some sulfa compounds, such as *p*-aminomethylbenzenesulfonamide and 3', 5'-dibromosulfanilamide, which are not inhibited by *p*-aminobenzoic acid. The suggestion would naturally be made that these might be inhibited by the compound corresponding to *p*-aminobenzoic acid which, in the case of the former product, would be the *p*-aminomethylbenzoic acid. However, studies by Lawrence (58) and others have demonstrated a lack of antagonism between these compounds, so that it is necessary to postulate some other mechanism, provided it can first be demonstrated that organisms become resistant to these compounds in the same way as they do to the classical *p*-aminobenzene sulfonamide types. There is a gap in our knowledge here which needs to be filled.

A phenomenon which cannot be ignored in explaining the mechanism of fastness is that some organisms apparently cannot be made fast by any ordinary means. For example, Carpenter & Allison (59) found that their strains of gonococci acquired only a slight, if any, tolerance to sulfathiazole, although resistance to sulfanilamide was readily established. Sesler & Schmidt (51) report similar experiences, as do also a number of others (49, 50). What would appear to be needed here is a careful correlation between the *p*-aminobenzoic acid production of organisms in the resistant and sensitive states, as well as between normal organisms and those in which it has been demonstrated that resistance could not be developed. One should be able to demonstrate that in these latter their *p*-aminobenzoic acid production remained at very low levels. However, a complication in the easy acceptance of the *p*-aminobenzoic acid theory is that the compounds studied by Lawrence (58) mentioned above are fully effective against organisms that have been made completely resistant to the usual sulfa-drugs.

From the clinical standpoint an important question is whether sulfa-fastness developed *in vitro* will be accompanied by similar lack of sensitivity of the organism in the sick patient. The case report of Frisch *et al.* (42) clearly indicates that there is close correlation between the *in vitro* and the *in vivo* responses of the organ-

ism. Another comparable report on the pneumococcus is that of MacLeod & Daddi (43). Spink *et al.* (46) have carefully studied the correlation between the *in vitro* and *in vivo* responses to the sulfa compounds and find the two appear to be directly related. For the gonococci similar correlations have been made by Frisch *et al.* (60), Carpenter and co-workers (59), and Cohn's group (61).

The most important element in the development of clinical resistance is undoubtedly inadequate dosage. Practically all writers on the development of sulfa-fastness in gonorrhea emphasize that this is usually associated with self-medication at inadequate levels of dosage. A similar relation between low dosage and fastness exists for other organisms.

#### PENICILLIN-FASTNESS

Resistance to penicillin can occur just as it does to sulfonamides. Schmidt & Sesler (62) have demonstrated penicillin resistance in pneumococci, and have shown that it does not alter the sulfonamide sensitivity of the organisms. They report the work of others where the converse has been demonstrated to be true. Similarly, Spink *et al.* (46) have shown that staphylococci may become resistant to penicillin, although they do not believe that this has much clinical importance. Gallardo (63) examined 108 strains of staphylococci, of which 24 were either naturally resistant to penicillin initially or became penicillin-fast during the course of treatment. Curiously, fastness to penicillin was observed in both pathogenic and nonpathogenic strains, indicating here a lack of correlation between those particular attributes.

There is no reason to believe that the mechanism of the development of penicillin resistance is the same as that to sulfa compounds, particularly if the importance of *p*-aminobenzoic acid is granted, since penicillin is not significantly affected by this compound (64). Penicillin apparently blocks the growth of organisms by interfering with their process of division (65). It has only weak action on spores and very little effect on organisms in the resting phase. A very intriguing aspect of the penicillin action is that there is a considerable lag phase and that the action is not controlled by the number of organisms present (66). In this respect penicillin action resembles that of an enzyme rather than a compound which is used up in producing its physiological effect. An excellent review

of the mechanism of penicillin action has recently been published by Herrell (67).

There is much evidence that the recent suggestion of Cavallito, Bailey *et al.* (38, 39, 68) on the mechanism of antibiotic action is an important one. They have discussed the relationship of sulfhydryl groups to the activity of penicillin and have shown that various materials which contain this group are able to inactivate the antibiotic substance. In addition, they have extended their observations to show that a number of other antibiotic substances behave in a similar manner. Confirmation of the importance of the sulfhydryl grouping has been brought forward by Hauschka and his collaborators (69).

Todd (70) has studied the actual changes going on in bacterial solutions in the presence of penicillin. He has demonstrated that there is a relationship between the ability of penicillin to lyse the organisms and its antiseptic action. However, he points out that bacteriostasis or even death to the organisms can be produced without lysis, and he interprets the entire phenomenon as being part of a continuous chain of action in which bacterial multiplication, death, and lysis are produced consecutively through one mechanism. He points out that penicillin is much more effective in young cultures when active multiplication is going on. The actively multiplying organisms are more susceptible to the lytic action than are older cultures, so that if this lysis is causally related to the rapidity of multiplication, this should result in an unusual effectiveness of the penicillin, which is indeed the case. This may help to explain, as he points out, why penicillin is so much more effective an antiseptic compound than are chemicals which lyse organisms by less specific mechanisms.

The question of how organisms can become fast against penicillin cannot be answered in any simple way. Demerec (71) has shown that the resistance to penicillin persists through more than twenty broth transfers. He postulates two possible mechanisms for the development of penicillin-resistant organisms: (a) that resistance is an acquired characteristic which develops through the interaction between bacteria and penicillin when the two are in contact with each other; and (b) that resistance is an inherited characteristic which originates through mutation and its origin is independent of penicillin treatment.

It would seem that the first possibility is a relatively unpromising one since it implies a selective persistence of more resistant organisms. This is in essence the theory, as has been discussed in relation to sulfa actions, of the drug's weeding out the less resistant organisms and leaving a new population derived from only the more resistant survivors. Such a theory seems to be inadequate because the resistance which can eventually be developed is far beyond that possessed by any individual organism present in the original culture at the time of first exposure to the antibiotic substance.

Demerec's second theory (71) involves assumption of the occurrence of mutations which radically modify the resistance of the organism through introducing into it new characteristics. At first glance there might be some hesitation about accepting the theory that such mutations continuously occur, in view of the common concept that mutations are extremely scarce and infrequent events. However, it must be remembered that the total number of bacteria present in a culture runs into astronomical figures, and that it is entirely possible that mutations are frequent enough in an organism as simple as the bacterium to permit the required changes in its protoplasm under the conditions of study. Inasmuch as many mutations are probably occurring in addition to those which are observed as affecting penicillin resistance, it would follow that these may be much more frequent in organisms at this level of development than they are in higher ones.

Spink & Ferris (35, 36) reported that staphylococci which had been made resistant to penicillin produced an inhibitor for it. However, this is not universally true since they also observed four strains which had been made highly resistant by exposures *in vitro*, but which were apparently lacking in any inactivator of the antibiotic.

McKee & Houck (72) have reported that increased resistance to penicillin and loss of virulence are accompanied by a slowing in the rate of growth of organisms and variations in the types of colonies. However, they did not find in pneumococci any change in the bile solubility or in type specificity, nor were there alterations in the fermentative reactions.

Of clinical importance in penicillin therapy, just as in that with sulfa-compounds, is whether *in vitro* resistance to the antibiotic

is indicative of resistance *in vivo*. Warner & Amluxen (73) reported that a hemolytic *Staphylococcus aureus* which was resistant to penicillin *in vitro* resisted the same concentrations *in vivo*. Similar observations have been reported by Schmidt & Sesler (62) for pneumococci, and would seem to be generally applicable. Penicillin-fastness once induced apparently may persist over prolonged periods of time, although this again is much influenced by the characteristics of the specific strain. There is also a marked difference between strains in the ease with which such fastness can be developed. Reports have been made of fastness developed in hemolytic *Staphylococcus aureus* (71, 73), streptococci (67), pneumococci (62), gonococci (64), and probably many others.

The prevention of the development of penicillin-fast strains is very important if penicillin therapy is to continue as highly successful as it is at present. Apparently most organisms which are at all sensitive to penicillin can be killed by it at concentrations which are within attainable therapeutic levels. If the dosage is so adjusted that effective concentrations are used from the outset, then the organisms are killed quickly before an opportunity is afforded for their passing over into the resistant state(74).

#### THE MODE OF ACTION OF SULFONAMIDES

The emphasis currently placed on antibacterial agents of natural origin detracts but little from the interest in the mode of action of the sulfonamides. In the decade since introduction of this class of therapeutic agents many general theories have evolved to explain how they achieve inhibition of bacterial growth. In two recent publications Henry (75, 76) has compiled for those with a special interest the extensive and varied data constituting our knowledge on how sulfonamides act. The present review draws heavily on this source<sup>1</sup> in an attempt to meet the needs of physiologists interested principally in the broad aspects of the subject.

An important question is whether sulfonamides are active *per se* or first must be converted into an active form. Regarding this it will be recalled that 4-sulfamido-2',4'-diaminoazobenzene (Prontosil) was first patented and marketed before the discovery

<sup>1</sup> Because the monograph by Henry contains practically every literature reference on the subject, only those appearing subsequently or of key importance will be referred to specifically.



in 1935 that its activity stems from the sulfanilamide into which the parent compound is largely or wholly converted. However, even the high activity of sulfanilamide did not suffice to establish it as the ultimate form responsible for the antibacterial activity. Mayer & Oechslein (77) observed that *p*-aminobenzenesulfonamide is even more active *in vitro* against some bacteria and postulated that sulfanilamide is antibacterial only after its oxidation. This "precursor" hypothesis has not been borne out by subsequent studies, notably those showing that oxidation products of sulfanilamide are not antagonized by *p*-aminobenzoic acid. Furthermore, a sulfonamide devoid of the free amino group in the para position has recently been shown to be active (78); this cannot possibly give rise to *p*-aminosulfonamide through oxidation. The failure of this hypothesis led to discarding the "anticatalase" theory (79), according to which sulfonamides act by a chain of events leading finally to self-destruction of the bacteria. The theory is nevertheless of interest because it made an enzyme the target of the sulfonamide effect. Henry has succinctly described the theoretical steps in the process as follows: (a) sulfanilamide is oxidized by the bacteria to *p*-hydroxylaminobenzenesulfonamide; (b) the latter inhibits catalase; (c) hydrogen peroxide resulting from bacterial metabolism, normally decomposed by catalase, now accumulates; and (d) when sufficient peroxide accumulates the bacteria are destroyed or their growth is hindered.

Sevag & Shelbourne (80) showed experimentally that *p*-hydroxylaminobenzenesulfonamide does not inhibit catalase under all conditions and that *Streptococcus pyogenes*, which sulfanilamide will inhibit, may grow in the absence of sulfanilamide without forming peroxide in detectable quantities. Moreover, *p*-aminobenzoic acid will not inhibit *p*-hydroxylaminobenzenesulfonamide.

The striking antagonism by *p*-aminobenzoic acid to the then-known sulfonamides led Woods & Fildes (81) to enunciate the theory that sulfonamides interfere with the utilization of *p*-aminobenzoic acid in the bacterial cell. Fildes (82) pictured the structurally similar sulfonamide as displacing *p*-aminobenzoic acid from the surface of an enzyme molecule, thereby disrupting a presumably essential phase of the cell's metabolism and causing bacteriostasis. Much experimental data on the action of sulfonamides fits neatly into this theory. *p*-Aminobenzoic acid has been shown to be

an "essential metabolite" for many and various organisms which are sensitive to sulfonamides. The acid, however, has been isolated thus far only from yeasts and one strain of diphtheria bacilli. The ability of *p*-aminobenzoic acid to antagonize the commonly known sulfonamides has been widely confirmed under a variety of experimental conditions, both *in vitro* and *in vivo*. The antagonism is competitive, i.e., bacteriostasis or growth may be obtained by altering the ratio of *p*-aminobenzoic acid to sulfonamide over a wide range of concentrations. However, the amount of the substance required is not the same for all sulfonamides and, in fact, varies in direct proportion to the bacteriostatic potency of the drug. Thus, the same absolute amount of *p*-aminobenzoic acid is required to counteract the minimum bacteriostatic concentrations of different sulfonamides, e.g., against *E. coli*,  $5 \times 10^{-7}$  M *p*-aminobenzoic acid just restores growth in the presence of sulfanilamide, sulfaguanidine, sulfapyridine, sulfathiazole, and sulfadiazine in concentrations of 2500, 500, 20, 4, and  $4 \times 10^{-8}$  M, respectively (83).

The Woods-Fildes theory gained wide support because of the immense amount of data compatible with it and because incompatible observations were left unexplained. During the past year the latter have constituted a groundswell which appears to have practically set aside the theory without, unfortunately, definitely establishing another in its place. The evidence against the theory that *p*-aminobenzoic acid (or any similar antagonist) is an essential metabolite competing with the sulfonamide for an enzyme is as follows: (a) Although *p*-aminobenzoic acid may be related to the normal intermediary metabolism of the cell, this relationship is not necessarily connected with the antagonism of the sulfonamides. Sulfonamides block enzyme systems which clearly do not involve *p*-aminobenzoic acid although the latter will antagonize the sulfonamide block. (b) Sulfonamide inhibition has been observed which is not antagonized by *p*-aminobenzoic acid, notably the respiration of the fertilized sea urchin egg (84). (c) Structural similarity to the sulfonamides is not a prerequisite for antagonizing their effect.

To these generalizations must be added the failure of *p*-aminobenzoic acid to antagonize three types of sulfonamides recently described (78). Examples of these types are (a) *p*-aminomethylbenzenesulfonamide ("Marfanil," "Sulfamylon"), which differs

from sulfanilamide only in having its amino group separated from the aromatic nucleus by a methylene group, (b)  $N^1$ -(3,5-dibromophenyl)-sulfanilamide, in which a dibromophenyl group replaces a hydrogen of the amide radical of sulfanilamide, and finally (c) 3',5'-dibromobenzenesulfonanilide, which lacks the free amino group of the sulfanilamide derivative just named. Schreus (85) first observed the failure of *p*-aminobenzoic acid in the case of Marfanil and explained it by postulating that *p*-aminomethylbenzoic acid was the logical antagonist according to a reasonable extension of the Woods-Fildes theory. By actual test Lawrence (58) showed that the aminomethyl acid was equally ineffective even when three moles of acid were used for each mole of the sulfonamide at the latter's limiting bacteriostatic concentration ( $3.6 \times 10^{-4}M$ ). The theory clearly fails in the cases of the dibromoanilides; *p*-aminobenzoic acid should, but does not, antagonize sulfanilyl dibromoanilide which has a full amino group, while the desamino compound should not be active. One common characteristic stands out to contrast these compounds with the "conventional" sulfonamides, i.e., they are bactericidal at virtually the same concentrations which are just bacteriostatic. This clearly indicates that their mode of action differs from that of sulfanilamide by some means to be revealed by future study. Probably a fruitful approach will be to compare these compounds with the older sulfonamides as to their effects on bacterial respiration.

In this connection, Sevag & Shelbourne (80) support the view that the sulfonamides act by inhibiting cell respiration and particularly that phase of the respiratory process which provides energy for growth. They observed inhibition of respiration of the cells of *Streptococcus pyogenes* which were not growing or dividing. When sulfonamide was added to growing cells, respiration and growth were inhibited to the same degree. They interpret their observations as showing that sulfonamides block the energy-liberating enzyme reactions which are necessary for growth and cell multiplication. They feel there is evidence of the formation of either an inactive "enzyme analogue" or "drug-protein-coenzyme complexes," neither of which can oxidize substrates such as glucose. With the failure of respiration, growth fails. The recent and clear-cut data of Fisher, Henry & Low (84) on the respiration of sea urchin eggs show that in the fertilized eggs respiration paralleled cell division irrespective of the extent of the inhibition induced by

the sulfonamide, the concentrations of which varied over a hundred-fold.

Although it must be recognized that bacterial metabolism involves many other enzyme reactions besides the reversible oxidation-reduction system responsible for respiration, the concomitant and proportional failure of both respiration and growth is suggestive of a causal relationship. In marshalling support for this hypothesis as a substitute for the discredited Woods-Fildes theory, Henry states: "The identities of the inhibited respiratory enzyme or enzymes responsible for the growth-inhibition are not definitely known, but it has been shown that sulfonamides inhibit certain dehydrogenases and carboxylase, and it seems fairly certain that it is inhibition of this coenzyme-protein type of enzyme which secondarily results in growth-inhibition."

In their effect on cell respiration the sulfonamides behave so similarly to narcotics that like the latter they too must be regarded as indifferent inhibitors. It seems reasonable that both act by becoming adsorbed onto the protein molecules of specific respiratory enzymes. The narcotics are known to inhibit the dehydrogenases. If sulfonamides also affect this protein-coenzyme system they may do so in any one of a variety of ways, all involving adsorption. That is, possibly by virtue of chemical similarity there may be adsorption onto the coenzyme, the protein molecule of the enzyme, or onto the substrate. There are no data to support any postulate in this regard since it is known only that normal cell division hinges upon the delivery of energy from an unknown but specific portion of the cell's total oxidative metabolism.

The current view of sulfonamide action, therefore, is that this class of drugs disrupts the oxidative production of energy necessary for cell growth, probably by an indifferent adsorptive interference with the normal catalytic functioning of dehydrogenases.

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